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TUMORS OF MUSCLE TYPE

REPORT OF A GROUP OF CASES, WITH SPECIAL REFERENCE TO METASTASIS OF LEIOMYOSARCOMA TO THE BRAIN

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PHILADELPHIA

Muscle tumors have been termed leiomyomas, or smooth muscle tumors, and rhabdomyomas, or striated muscle tumors. They may be benign or malignant.

The incidence of muscle tumors varies with the type. Benign myoma occurs very frequently, especially in the uterus. Gusserow [1] stated that 38.8 per cent of all women between the ages of 30 and 40 have myoma uteri. The tumors may be submucous, subserous and intramural in location, and are usually multiple. They may occur in the cervix, vagina, round ligaments, broad ligaments and pelvic fasciae. Reports of the incidence of malignant leiomyoma vary. Frequently statistics of its occurrence are based on the discovery of local areas of increased cellularity in the tumor, without evidence of general symptoms, metastasis or recurrences. As a result of this method of tabulation, reports are made in which it is asserted that 10 per cent of all uterine myomas are malignant. Leiomyosarcoma is much rarer than is generally believed. In twenty years of observation, Ewing [2] encountered three malignant uterine myomas with general metastasis and two with local recurrence. Gardner [3] found one case of leiomyosarcoma in the Boston City Hospital in twenty years. This coincides with the finding of two cases among 18,077 necropsies in the Philadelphia General Hospital in the course of eleven years. Leiomyosarcoma occurs usually after the menopause, though Ewing stated that polypoid myoma of the cervix is usually malignant at all ages.

Rhabdomyoma occurs infrequently. It is usually found in early life. The most common sites are the kidney, heart, vagina, cervix and testicle. Rarer sites are the esophagus, stomach, tongue, parotid gland, breast, prostate and skeletal muscles of the body. Rhabdomyosarcoma is seldom encountered.

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From the Division of Pathology of the Laboratories of the Philadelphia General Hospital.

1. Gusserow: Die Neubildungen des Uterus, ed. 1, Stuttgart, Ferdinand Enke, 1885, p. 269.

2. Ewing: Neoplastic Diseases, ed. 2, Philadelphia, W. B. Saunders Company, 1922, p. 207.

3. Gardner: J. M. Research **36**:19, 1917.

ETIOLOGY

No definite proof regarding the etiology of muscle tumors has been presented. The cell inclusion theory of Cohnheim [4] is the one most commonly mentioned. He derived his theory of the origin of all tumors from observation of a case of congenital myosarcoma of the kidney while he was working at Breslau.

Embryologically, muscle tissue arises from mesoderm. Smooth muscle arises from undifferentiated mesenchyme. Figures 1 *A* and *B* shows the source of this tissue. The stellate cells of the mesenchyme, shown in figure 1 *C*, become spindle-shaped and are connected by cytoplasmic bridges. Figure 1 *D* shows the coalescence of the granules in

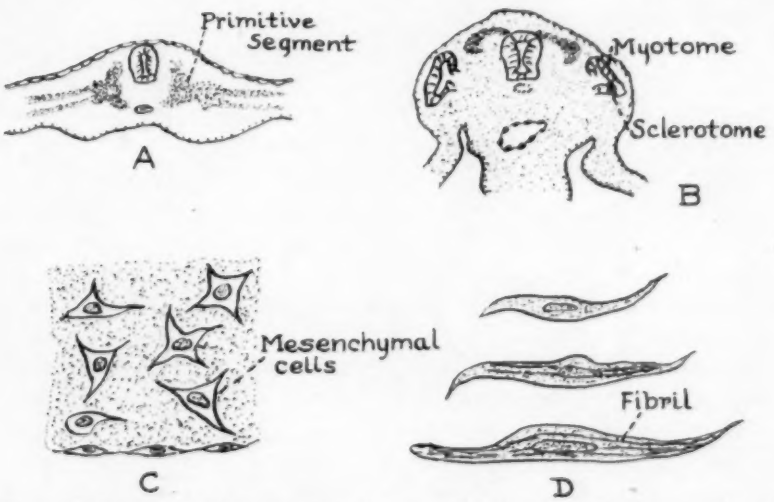

Fig. 1.—Diagrammatic representations modified from Prentiss and Arey (Embryology, ed. 2, Philadelphia, W. B. Saunders Company): *A*, chick embryo at two days; *B*, human embryo at three weeks; *C*, mesenchymal tissue, and *D*, developmental myoblast.

the superficial cytoplasm of the myoblast to form coarse, noncontractile myoglia fibrils. Later, these divide longitudinally to form fine myofibrils, thus giving the cell its longitudinally striated appearance. The cytoplasmic processes develop into white connective tissue fibers, which bind the smooth muscle cells into bundles.

Prentiss and Arey [5] listed the following methods of increase in the number of smooth muscle cells in the embryo: (1) formation of new cells from mesenchyme, (2) transformation of interstitial cells into

4. Cohnheim: Cohnheim's Lectures, London, New Sydenham Society, 1889, sect. 1, mem., p. XIII.

5. Prentiss and Arey: Embryology, ed. 2, Philadelphia, W. B. Saunders Company, 1918, p. 292.

muscle fibers and (3) multiplication of their nuclei by mitosis in the more advanced fetal stage. Thus, smooth muscle tumors may arise in the adult by the unrestrained growth of misplaced persistent mesenchymal cells.

Ewing [6] stated that the widespread occurrence of myomas in mature life and the presence in many cases of heterotopic inclusions point clearly to an embryonal origin. He believes that pure fibromyoma uteri results from the malformation of the genital organs from the müllerian ducts. Rosger [7] and Kleinwachter [8] believe that myoma arises from the walls of blood vessels. Muller [9] and Larkin [10] are of the opinion that myoma of the kidney arises from fragments of the capsular tissue.

Embryologically, striated muscle arises from the myotome, shown in figure 1 *B*. The muscles of the head are exceptions; they arise from mesenchyme. There are two theories concerning the formation of striated muscle fibers: 1. The myoblast of the myotome elongates and by repeated mitotic division becomes multinucleated. 2. The myoblasts unite to form single, elongated muscle fibers.

Some investigators believe that the micelle of the myofibril occurs in the ovum; others,[11] that the myofibrils arise from the mitochondrial rods and filaments, without a granular stage. Godlewski [12] believes that the fibrils pass through a granular stage as described in the development of the smooth muscle cell. Wolbach [13] thinks that the fibrils arise by connection of centrioles. Baldwin [14] regards the myofibril as a differentiated product of the muscle cell, the homologue of the connective tissue fiber.

Three theories of the etiology of rhabdomyoma are possible: (1) the cell inclusion theory of Cohnheim, (2) that of development of the striated muscle cell from the fibroblast through metaplasia and (3) that of differentiation from the smooth muscle cell. The latter possibility is suggested by the work of Carey,[15] who succeeded in transforming the normal smooth muscle cells of the urinary bladder into striated muscle by repeated filling and emptying of the bladder. On the other hand, Reyder stated that rhabdomyoma of the heart is persistent embryonal tissue and not a true neoplasm.

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6. Ewing (footnote 2, p. 213).
7. Rosger: Ztschr. f. Geburtsh. u. Gynäk. **18**:131, 1890.
8. Kleinwachter: Ztschr. f. Geburtsh. u. Gynäk. **9**:68, 1883.
9. Muller: Virchows Arch. f. path. Anat. **145**:339, 1896.
10. Larkin: J. M. Research **6**:25, 1901.
11. Morceau: Bibliographie Anatomique, Paris, 1902, vol. 10, p. 1.
12. Godlewski: Arch. f. mikr. Anat. **3**:60, 1902.
13. Wolbach: Anat. Rec. **37**:255, 1928.
14. Baldwin: Ztschr. f. allg. Physiol. **14**:146, 1912.
15. Carey: Am. J. Anat. **29**:341, 1921.

LEIOMYOMA

Histologically, leiomyoma consists of irregular bundles of cells, frequently arranged in whorl formation. The individual cells are spindle-shaped, but rather thicker and shorter than normal smooth muscle cells. They have centrally located, relatively long, oval, chromatic nuclei. The cytoplasm is less acidophilic than that of the normal analogue. Mallory [16] considered the myoglia fibrils described by Heidenhain the most important factor in the differentiation of smooth muscle cells from

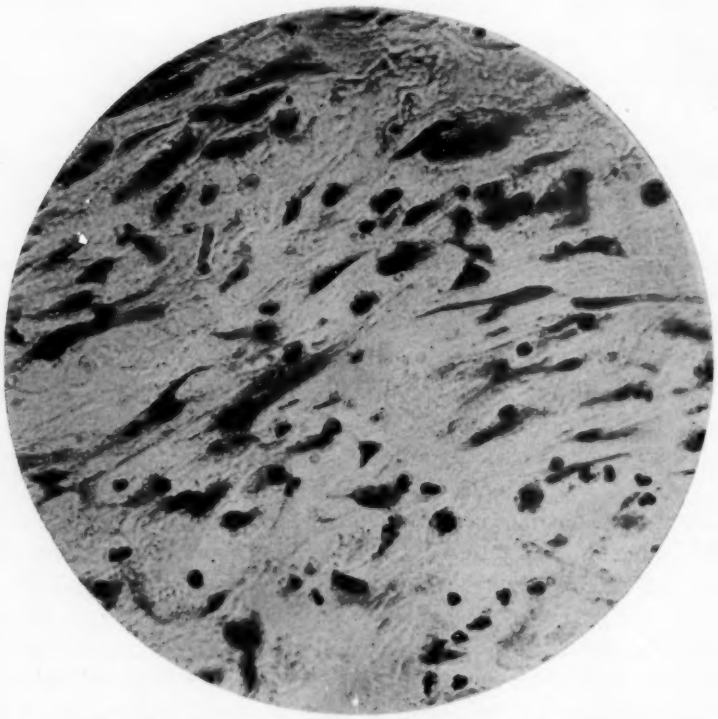

Fig. 2.—Photomicrograph showing intracellular fibrils of smooth muscle cells; × 520.

fibroblasts. These fibrils, situated within the limiting membrane, fuse at the end of the cell to form coarse fibrils, while the fibrils of the fibroblast spread out in fan shape some distance from the cell. Figures 2 and 3 picture this essential difference. Differential stains, such as Mallory's phosphomolybdic acid, aniline blue, orange G or van Gieson's alum hematoxylin, acid fuchsin, trinitrophenol, can be used with assurance in distinguishing the muscle from the connective tissue.

16. Mallory: Principles of Pathologic Histology, ed. 1, Philadelphia, W. B. Saunders Company, 1920, p. 305.

The following five cases of leiomyoma were found incidentally at postmortem examination:

CASE 1.—A white woman, aged 70, died of intraventricular hemorrhage. In the kidney was found a tumor composed of smooth muscle cells arranged irregularly. Histologically, it was a leiomyoma. It had produced no symptoms.

CASE 2.—A white man, aged 80, died of bronchopneumonia and hemorrhagic infarction of the kidney. A small, gray nodule was found in the cardiac end of the stomach. It was 1.8 cm. in diameter and shelled out readily. Histologically, it was a leiomyoma. It had produced no symptoms.

Fig. 3.—Photomicrograph showing the fan-shaped arrangement of extracellular fibroblastic fibrils; × 520.

CASE 3.—A white woman, aged 79, suffered from multiple neurologic phenomena, shown by necropsy as due to convolutional atrophy and arteriosclerosis of the basal ganglions. A round mass was found in the ileum projecting into the lumen. The overlying mucosa was intact. No surrounding induration was present. Histologic examination showed this to be a leiomyoma.

CASE 4.—A colored woman, aged 53, died of diabetic gangrene of the right leg. Two small nodules were found in the cardiac end of the stomach. They were well circumscribed and lay loosely under the mucosa. Histologically, they were leiomyomas.

CASE 5.—A white woman, aged 76, died of cerebral hemorrhage. A tumor 8 mm. in diameter was found movable in the muscle of the gastric wall. It was a soft, well circumscribed leiomyoma.

LEIOMYOSARCOMA

Arthur Hertzler [17] expressed the belief that malignancy in myoma of the uterus is due to hemorrhage into the tumor. He listed the changes as follows: (1) obliterating endarteritis, (2) hyaloid degeneration of the wall of the blood vessel, (3) degeneration of the surrounding tissue, (4) free hemorrhage and (5) rapidly developing sarcoma from hemorrhagic tissue. This idea has met with much objection.

The cells of the malignant leiomyoma are shorter and rounder than those of the benign tumor. The nuclei are massive and hyperchromatic. Giant cell forms may exist. The stroma is scanty. The walls of the blood vessels are defective. Evans [18] believes that the occurrence of many mitotic figures is a reliable sign of malignancy. Proper and Simpson [19] classified malignant leiomyomas into three groups: (1) those closely resembling leiomyomas, (2) those having short spindle-shaped cells with oval nuclei and (3) those showing great variation in cell morphology. He believes that malignancy increases progressively through the groups.

CASE 6.—A colored woman, aged 47, was admitted to the hospital complaining of intermenstrual bleeding. The last menstrual period occurred in October, 1930. In November, 1930, she passed large clots. Following this, the periods were irregular, and a thick discharge of foul, yellow material occurred, occasionally intermixed with blood. Cramps occurred in the abdomen after meals, inducing nausea and vomiting. In January, 1931, the patient noted dyspnea on exertion, severe night sweats and diurnal and nocturnal frequency of urination.

The lungs were normal. The heart was slightly enlarged to the left. Presystolic and systolic murmurs could be heard over the entire precordium. The abdomen was distended by a hard, nodular mass, which arose in the pelvis and extended to the umbilicus. It appeared to be a part of the uterus.

Roentgen study revealed a dense, circular shadow in the left lower hemithorax at the level of the ninth rib in the midclavicular line. The right dome of the diaphragm was higher than normal and was obliterated by the presence of fluid.

Necropsy revealed multiple white, firm nodules in the uterus, enclosing areas of soft hemorrhagic tissue. There were secondary nodules in the lungs and liver. The nodules in the lungs were firm, white and circumscribed; that in the liver was necrotic, and had ulcerated through the diaphragm into the right lung.

Histologically, the cells of the soft hemorrhagic areas in the uterus were larger than those of the surrounding tissue. The nuclei were fairly large and varied in shape, some being spindle-shaped, some round and some oval. A few bizarre cells contained multiple nuclei. The cytoplasm was small in amount and irregularly fibrillar.

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17. Hertzler: J. A. M. A. **71**:1040, 1918.
18. Evans: Surg., Gynec. & Obst. **30**:225, 1920.
19. Proper and Simpson: Surg., Gynec. & Obst. **29**:39, 1919.

In reviewing the literature, I was unable to find a record of a myoma occurring as a primary or as a secondary neoplasm of the brain. If this survey is correct, the following report of a case describes the first recorded instance of leiomyosarcoma that metastasized to the brain:

CASE 7.—An emaciated, senile white man of 65 was admitted to the hospital, complaining that he had had "failing health" since the occurrence of a "stroke" in 1928. Further history could not be obtained.

The liver was enlarged to a level 4 fingerbreadths below the costal margin. A hard, fixed, circumscribed nodule about 7 cm. in diameter could be felt at the lower border of the liver, about 4 cm. to the right of the umbilicus. It moved with respiration.

Fig. 4.—Photograph showing nodule of leiomyosarcoma in the occipital lobe of the brain.

Roentgen examination revealed a slight six hour retention due to a mass in the stomach, which was interpreted as carcinoma.

The urine contained a trace of albumin and many leukocytes. The red blood cell count was 4,400,000; the hemoglobin content was 12.7 Gm.; the leukocyte count was 17,200, with 81 per cent polymorphonuclears. The Wassermann reaction of the blood was negative. The blood sugar determination was 113 mg., and that of blood urea nitrogen was 20 mg. Fractional gastric analysis showed no free hydrochloric acid; total acid was 15, 15, 19, 22, 19, 17, 22 and 29 mg. Lactic acid was present.

Necropsy revealed a primary leiomyosarcoma of the left kidney with metastases to both lungs, right kidney, suprarenal glands, ileum, mediastinal and mesenteric lymph nodes and brain. The right kidney weighed 680 Gm. It was irregular and

nodular, but freely movable in the perirenal fat. It was firm and cut with increased resistance. It was homogeneous and of a uniform yellow color. In the upper pole was a round area 4 cm. in diameter, composed of deep yellow, necrotic material, putty-like in consistency. No renal tissue was present that could be recognized as such grossly. The nodules in the lung were numerous, varying in size from 4 mm. to 3 cm. in diameter. They were all firm, resistant and yellow.

The brain weighed 1,520 Gm. It was large but of normal shape. The pia-arachnoid was thickened, and showed fibrosis of the interpeduncular space. The cortical convolutions were swollen, and the blood vessels were congested. The pons, medulla and cerebellum appeared normal. The ventricles were definitely

Fig. 5.—Photomicrograph of leiomyosarcoma of the brain showing whorl formation; × 69. For high power magnification, note figure 2.

dilated. The basis pontis contained a scar on the right side resulting from an old thrombotic lesion. Practically the entire right half of the basis pontis was degenerated. When the left occipital lobe was cut through, a nodule was seen deep in the subcortex. This lay immediately posterior to the calcarine cortex, and the softening around it involved the latter structure. The nodule measured 2 cm. in longitudinal diameter and 0.5 cm. in transverse. It was firm and yellowish green, and showed central necrosis. It appeared encapsulated owing to softening of the white matter about it. This is seen in figure 4. Examination of the tumor under low power, with the 16 mm. objective, presented a whorl appearance, shown in figure 5.

Examination under high power magnification, with the 4 mm. objective, showed the cells to be of irregular spindle shape. With toluidine blue stain, the cytoplasm stained light blue and presented longitudinal striations. The nuclei were oval, elongated and centrally located, and contained a central spherical nucleolus. Both stained dark blue. Figure 2 illustrates these cells.

RHABDOMYOMA

Histologically, the picture of rhabdomyoma varies, depending on the degree of maturity of the cells comprising the tumor. The mature type

Fig. 6.—Photomicrograph showing rhabdomyosarcoma in the left suprarenal gland; × 69.

of tumor consists of irregular bundles of striated muscle; the immature type, of single cells or small groups of cells with prominent nuclei and scanty cytoplasm. The cells are shorter and rounder, and resemble smooth muscle cells. Cross-striations may be rare, but areas can always be found where the cells show characteristic striations. The mature type of cell is generally found in the benign tumor; the immature type is more likely to be malignant. The stroma may be loose adult connective tissue or a more embryonal myxomatous or sarcomatous type. Vascularity is usually prominent. The following report represents the

only case of rhabdomyosarcoma found among 18,077 necropsies at the Philadelphia General Hospital in eleven years.

Case 8.—In November, 1929, a white woman, aged 18, complained of a loss of sensation over the left hip. One month later, she began to have pain in the left side of the chest and noticed lumps over the entire body. During July, 1930, a gradual onset of paralysis of the legs occurred. In January, 1931, amenorrhea began.

Both pupils were dilated. Cervical adenopathy was present. There was increased vocal resonance, and râles were heard throughout the chest. The heart was displaced upward; the rate was rapid and irregular, but no murmurs could

Fig. 7.—Photomicrograph showing cross-striations in rhabdomyosarcoma; × 520.

be heard. The blood pressure was 104 systolic and 72 diastolic. Ascites was present. Four large nodes were palpable in the anterior abdominal wall. The muscles of the legs were atrophic. The deep tendon reflexes were absent. The course of the illness was progressive, and the patient died on Sept. 1, 1931.

Necropsy revealed a white woman, 170 cm. in length and 75 pounds (34 Kg.) in weight, with scoliosis to the right and bed sores over the sacrum. The heart weighed 200 Gm. and contained numerous nodules throughout the myocardium. One nodule, 1 cm. in diameter, was present in the posterior aspect of the septum; there was another in the interventricular septum near the apex. They were glistening, white, smooth and friable, resembling pearls. The lungs showed numerous abscesses. The left kidney contained a large, nodular tumor in the upper pole, 3

cm. in diameter. It was irregularly round, soft, glistening and friable. The right kidney was the seat of multiple abscesses. The capsule of the spleen contained many patches. The liver showed chronic, passive congestion. The small bowel had numerous small tumors situated in the serous coat. A large tumor involved the pancreas, diaphragm, omentum, right kidney, aorta, spinal column, dura of the cord, left suprarenal gland and left ovary.

Histologically, the tumor cells of the left suprarenal gland were most characteristic. They corresponded to the immature type of rhabdomyosarcoma, but showed cross-striations. The tumor cells of the other organs showed a rather marked degree of necrosis. Figures 6 and 7 show the metastatic tumor in the suprarenal gland under low and high power objectives.

SUMMARY

The incidence of muscle tumors varies with the type. Leiomyoma occurs frequently, especially in the uterus. Leiomyosarcoma is less frequent, according to my studies, than is generally claimed. What appears to be the first case of metastasis of leiomyosarcoma to the brain is described. Rhabdomyoma occurs very rarely. Rhabdomyosarcoma is rare. The diagnosis of muscle tumors depends on close observation of the type of cell, i. e., the finding of spindle-shaped cells arranged in whorl formation or of cross-striations in large, irregular cells. Mallory's and van Gieson's differential stains are of diagnostic aid. The possible theoretical origins are enumerated.

LOCAL TISSUE IMMUNITY

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Immunologic investigations of recent years place increasing emphasis on the direct part played by the mesenchymal tissues in resistance to infectious diseases, and as a result cellular reactions of inflammation are being studied with renewed interest in the attempt to understand their fundamental significance in the general mechanism of defense. The idea of localization of infection as a definite defensive factor has assumed greater importance in the minds of many students of the problem, although the importance of general humoral elements is not denied. The conception has developed that increased resistance to certain infectious agents may be largely local, due to a more effective response of local tissues to the invading micro-organism. This notion, while not new, has been emphasized particularly by Besredka,[1] who has stimulated renewed interest in the problem of local immunity. New facts have resulted from this interest which not only strengthen the view that such an immunity actually exists, but also help to explain its mechanism.

In this paper experiments are reported which further support the idea that local immunity can be acquired.

There is at present some confusion regarding what is meant by the term local immunity. Besredka,[2] for example, defined it as "an immunity without the obligatory participation of antibodies." Gay,[3] on the other hand, defined the condition as a "locally superior mechanism for the disposal of a particular micro-organism," and stated that it may be demonstrated "either by the local presence of antibodies before their appearance elsewhere in the body, by their local presence in greater concentration than elsewhere, or by a superior method of direct disposal of bacteria in the particular area in question." Opie[4] interpreted local immunity after a previous sensitization to a specific antigen or bacterium as a local hypersensitivity that is manifested by an acute inflammation having the essential features of a local anaphylactic reaction, and tending to retard the entrance of bacteria or their noxious products

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1. Besredka, A.: Compt. rend. Soc. de biol. **88**:1273, 1923.
2. Besredka, A.: Local Immunization, Baltimore, Williams & Wilkins Company, 1927.
3. Gay, F. P., in Jordan, E. O., and Falk, I. S.: The Newer Knowledge of Bacteriology and Immunology, Chicago, University of Chicago Press, 1928.
4. Opie, E. L.: J. Immunol. **17**:329, 1929.

into the blood stream. This retardation, he assumed, is brought about by the local accumulation of antibodies, which fix the antigen or bacteria at the site of inoculation, thus localizing the infectious agent and preventing its dissemination to more vital organs.

Regardless of differences in point of view concerning the actual mechanism of local immunity, most of the workers agree as to the existence of a localized condition that brings about an increased resistance to a specific micro-organism. This does not necessarily eliminate or minimize the importance of a generalized response.

HISTORICAL EVIDENCE FOR THE EXISTENCE OF LOCAL IMMUNITY

Fehleisen [5] in 1883 was probably the first to note evidence of experimental local immunity. He observed a locally increased resistance while reproducing erysipelas in animals and human beings who had recovered from previous attacks of the disease. Meierowitsch [6] in 1888 found that rabbits which had recovered from one attack of experimental erysipelas were protected from a second attack for from one to two months. As evidence that the immunity acquired after erysipelas is general as well as local, Roger [7] produced an attack of erysipelas in one ear of a rabbit, and after recovery had taken place, produced a second attack in the opposite ear, and found that it was followed by a rapid recovery or the formation of a small abscess. On the other hand, Gromakowsky [8] called attention to the absence of immunity against the streptococcus of erysipelas in the peritoneal cavity of animals previously immunized in the skin.

Cobbett and Melsome [9] produced both local and general immunity against erysipelas by subcutaneous inoculations of a pure culture of living streptococci into the ears of rabbits. They demonstrated the presence of local immunity by comparing the effects of inoculations of living streptococci into the ears of rabbits that had recovered from previous inoculations of the same micro-organism, with those of similar inoculations into normal rabbits. The response in the previously inoculated rabbits was manifested by an early local inflammatory reaction that subsided in from one to four days and the absence of general toxic effects. The control rabbits, on the other hand, presented a slow, progressive inflammatory reaction accompanied by general malaise and in many instances by death. The existence of a generalized immunity was demonstrated in two ways, first by producing an attack of erysipelas in the right ear and a few days after recovery producing a second attack in the left ear. The reaction was compared in extent and out-

5. Fehleisen: Aetiologie der Erysepelas, Berlin, T. Fischer, 1883.
6. Meierowitsch: Centralbl. f. Bakt. (ref.) **3**:406, 1888.
7. Roger, G. H.: Compt. rend. Soc. de biol. **42**:573, 1890.
8. Gromakowsky, D.: Ann. Inst. Pasteur **9**:621, 1895.
9. Cobbett, L., and Melsome, W. S.: J. Path. & Bact. **3**:39, 1896.

come with that of normal rabbits which had simultaneously been given the same quantity of streptococci. In half of the reinfected rabbits there were evidences of general immunity manifested as an early severe inflammatory reaction, which subsided in from three to four days. In a few instances, too, there were small abscesses as the end-result of the second attack of erysipelas. The second method was to inject streptococci into the peritoneal cavity and after recovery of the rabbit from this inoculation, to produce erysipelas in one ear. The course of the infection indicated that the rabbit had acquired an excellent general immunity, inferior to the local but superior to the general immunity produced by the inoculation of the opposite ear.

These investigators concluded that both local and general immunity resulted from the early inflammatory response, enhanced by the previous sensitization of the tissues. The lack of protection in the normal animals was interpreted as being due to the delay of the inflammatory reaction, which allowed the micro-organisms to multiply and produce their toxic products, which were not overcome by the phagocytes of the subsequent inflammatory reaction.

Römer [10] produced a local corneal immunity in the conjunctiva of one eye in rabbits by injecting small quantities of abrin. This local immunity he demonstrated by the resistance that the previously injected conjunctiva offered to further inoculation of abrin, while the opposite conjunctiva remained susceptible.

Noguchi [11] demonstrated a locally increased resistance to tetanus toxin in rats in which wounds were sutured with silk threads containing tetanus spores and treated with eosin, since the threads, when removed and transplanted in other rats or in the opposite sides of the same rats, caused fatal tetanus. He further showed that the leg previously resistant to the tetanus spores reacted very slowly to a subsequent inoculation of tetanus bacilli, whereas in the opposite leg or in normal rats the same quantity of bacilli produced a rapidly fatal outcome. Noguchi explained this local immunity as the result of a possible formation of antitoxins in the local connective tissues.

In 1905 Wassermann and Citron,[12] in testing the resistance to typhoid bacilli of animals immunized in the pleural cavity, peritoneal cavity and blood stream, noticed that the immunization was more marked if the bacilli were injected through the route previously used, and that this immunity was not dependent on the quantity of antibodies present in the blood serum. To explain this locally heightened resistance they postulated the idea of "Umstimmung," or retuning, of the local cells to an increased phagocytic activity.

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10. Römer, P.: Arch. f. Ophth. **52**:72, 1901.

11. Noguchi, H.: J. Exper. Med. **9**:291, 1907.

12. Wassermann, A., and Citron, J.: Ztschr. f. Hyg. u. Infektionskr. **50**:331, 1905.

Later, Wassermann and Ledermann [13] advised the application of killed cultures of staphylococci on infected wounds to prevent the development of complications. Similar observations were made by Levaditi,[14] who noticed that war wounds infected with streptococci quickly destroyed streptococci that were applied on dressings during the healing stage.

More recently, interest in the problem of local immunity has been stimulated by Besredka,[15] who in 1921 advanced a new theory to explain its mechanism. In this he suggested that local immunity is essentially a desensitization of certain receptive cells, which when immunized, become indifferent to specific micro-organisms, and allow them to be destroyed by the phagocytes. Although not definite as to where these receptive cells are located, he mentioned the reticulo-endothelial system as a possible location or source. He stated, furthermore, that this local immunity can be produced artificially by substances that contain the hypothetic agent, which he calls antivirus.[16] The application of this antivirus on or near the receptive cells produces an acquired local immunity without the intervention of antibodies. When the infection is present, this same antivirus acts as an immune serum in passive immunity, or directly produces in the tissues of the animal a medium in which the micro-organisms are incapable of multiplying, either because of desensitization of the receptive cells or because of a direct action on the bacteria present. To substantiate his ideas, the author described experimental work in animals and many clinical cases in which the antivirus had been used with favorable results.

In this country, Gay [17] has done much to establish local immunity as a definite entity. His work began with the production of experimental empyema in rabbits by intrapleural injections of a particular strain of streptococcus hemolyticus. He noticed under such conditions that the infection remained entirely local, although a general immunity was produced, as shown by the presence of agglutinins, opsonins and precipitins in the serum. The latter were demonstrable, however, only by a special serologic technic. Of more significance was his demonstration of the local morphologic changes produced in the pleural cavities of rabbits by the inoculation of various substances that stimulate definite cellular reactions, and the relation of these to the immunity which some of the rabbits had acquired.[18] From such experiments Gay concluded that the exudates containing large numbers of polymorphonuclear leukocytes were not protective when a minimal lethal dose was

13. Wassermann, A., and Ledermann, R.: Med. Klin. **7**:479, 1911.
14. Levaditi, C.: Compt. rend. Soc. de biol. **81**:1059, 1918.
15. Besredka, A.: Ann. Inst. Pasteur **35**:421, 1921.
16. Besredka, A.: Bull. Inst. Pasteur **28**:49 and 105, 1930.
17. Gay, F. P., and Stone, R. L.: J. Infect. Dis. **26**:265, 1920.
18. Gay, F. P., and Morrison, L. F.: J. Infect. Dis. **33**:338, 1923.

inoculated into the pleural cavity, whereas exudates containing larger numbers of clasmatocytes than polymorphonuclear leukocytes protected against as many as 200 M. L. D. of hemolytic streptococci. Therefore Gay concluded that the local acquired immunity was nonspecific and dependent on the high ratio of clasmatocytes to polymorphonuclear leukocytes. Later, however, he demonstrated that a more pronounced local pleural immunity could be secured when specific antibodies were added to the increased number of clasmatocytes.[19] Rivers and Tillett [20] showed also that protection against streptococci injected into the skin was far greater when the skin had been infiltrated twenty-four hours before or at the same time with the immune serum, than after similar treatment with normal serum or beef broth. Opie [21] observed that an antigen persisted at the site of inoculation in animals previously sensitized to that antigen, and suggested that the accumulation is due to the local presence of antibodies, which unite and fix the antigen at the site of inoculation.

Freedlander and Toomey [22] produced a nonspecific local immunity against Staphylococcus aureus in the abdominal walls of guinea-pigs, by the application of wet compresses of broth, mustard, saline solution, meat, peptone and 10 per cent horse serum. Their morphologic observations demonstrated an increased number of clasmatocytes in the subcutaneous tissues.

In summary, then, one may conclude that local immunity in varying degrees has been demonstrated in erysipelas, in experimental streptococcal empyema, during the process of healing of wounds, after nonspecific stimulation with foreign proteins and other substances that bring about an inflammatory process, after injection of killed cultures of streptococci and staphylococci into local areas of the skin and after inoculation of tetanus bacilli into wounds. In all of these cases the immunity has been either a combined local and general immunity, or a general immunity manifested in a local area by a heightened, rapid inflammatory response after a nonspecific stimulation of the local tissues, or a local immunity with a general immunity of lesser degree in other portions of the body. The presence of antibodies in the blood serum has been demonstrated in many instances, and serums have been prepared that increased the local defensive powers. In explaining the mechanism of local immunity, some have postulated a defensive system that is nonspecific and dependent only on the number of phagocytes; others, that the local area contains a greater concentration of antibodies, which when combined with the antigen bring about a positive chemotaxis. Practically all of the investigators of this field, however, agree that an early

19. Gay, F. P., and Clark, A. R.: J. Exper. Med. **52**:95, 1930.
20. Rivers, T. M., and Tillett, W. S.: J. Exper. Med. **41**:185, 1925.
21. Opie, E. L.: J. Immunol. **8**:55, 1923.
22. Freedlander, S. O., and Toomey, J. A.: J. Exper. Med. **47**:663, 1928.

inflammatory reaction and an increased phagocytic activity are constantly present.

THE EXPERIMENTAL PROBLEM

As can be seen, the problem of local immunity is still obscure, first as to its existence, second as to its independence from a general immunity and third as to the mechanism determining it. With these considerations in mind the following questions were formulated:

1. Is there such a thing as local immunity independent from general immunity?
2. If so, what is the mechanism?
3. How can this be demonstrated experimentally?

The following experiments were undertaken in the attempt to answer these questions:

1. A histologic study of the changes in the skin of normal guinea-pigs during the process of localized intradermal injections of killed cultures of S. aureus.
2. A comparison of the gross reactions of the skin to inoculations of a living, virulent culture of S. aureus in normal guinea-pigs, in those given previous intradermal injections of 0.85 per cent salt solution and those given local intradermal injections of a staphylococcal vaccine.
3. Observation of the changes and healing processes in the skin of the abdominal wall after excision of the area inoculated with a living, virulent culture of S. aureus in normal guinea-pigs and in those previously treated locally with a staphylococcal vaccine.
4. A study of the histologic changes occurring at hourly intervals from the fifth to the twenty-fourth hour after intradermal injection of a living, virulent culture of S. aureus into the skin of the abdominal walls of normal guinea-pigs, of those previously given intradermal injections of sterile salt solution and of those previously treated intradermally with staphylococcal vaccine.

MATERIALS AND METHODS

In these experiments, guinea-pigs weighing from 150 to 350 Gm. were used. The material used for inoculation was from a culture of S. aureus obtained from a large furuncle on the upper lip of a patient who had suffered from fever, chills and malaise of ten days' duration. The virulence of the organism was determined by inoculating guinea-pigs intradermally in the abdominal wall with 0.2 cc. of a twenty-four hour agar culture, diluted in 1 cc. of physiologic solution of sodium chloride (0.85 per cent NaCl). The necrosis of an area about 0.5 cm. in diameter or the death of the guinea-pig within ninety-six hours was taken as a criterion of virulence.

Three methods of inoculation were tried to see which would cause the most pronounced inflammatory reaction: viz., with the bacteria diluted in 0.85 per cent solution of sodium chloride; with the bacteria in a 1:500 solution of calcium

chloride, and with the organisms suspended in melted agar at from 45 to 50 C. Of these three methods, the first was found easiest to control; it gave as good results as the others and did not introduce complicating reactions; it was therefore adopted as a routine procedure. A twenty-four hour agar culture of S. aureus was suspended in 1 cc. of sterile salt solution and heated at 60 C. for one hour, after which the suspension was transferred to a tuberculin hypodermic syringe equipped with a no. 28 gage needle, and 0.2 cc. was inoculated intradermally into the right side of the previously prepared anterior abdominal wall. An area measuring about 4 by 2 cm. had been shaved, carefully washed with tap water and soap, rinsed with sterile water and finally painted with a weak solution of iodine in a mixture of equal parts of ether and alcohol.

In all, ten daily injections, about 1 cm. apart, were made, the first three into the right anterior abdominal wall, the next four into the midline and the last three into the left abdominal wall. Control animals were similarly given injections of 0.2 cc. of 0.85 per cent solution of sodium chloride. The guinea-pigs were then left undisturbed for twenty-five days, after which they, with normal animals, were inoculated with 0.2 cc. of a twenty-four hour growth of living S. aureus diluted in 1 cc. of sterile salt solution.

Histologic study was made of pieces of tissue cut from the inoculated areas after they had been fastened with bamboo pegs on square frames of cork as advised by W. Bloom,[23] fixed in Zenker's fluid plus solution of formaldehyde, embedded in celloidin, cut at from 10 to 15 microns and stained with hematoxylin, eosin and azure II (method of Maximow[24]). For the study of the bacteria, Gram's and Claudius'[25] staining methods were used on smears and sections. For the determination of fibrin, the specific stains of Weigert,[26] Kockel,[27] Wolff,[28] Unna,[29] Schmidt[30] and Wallace[31] were used. In staining for fibrin, sections of normal and previously inoculated skins during different hours of the inflammatory process were stained, with an equal number of sections of pneumonic lung that contained fibrin. The latter served as controls on the efficiency of the stains at the time they were used.

GROSS AND HISTOLOGIC CHANGES PRODUCED IN THE SKIN OF NORMAL GUINEA-PIGS BY TEN DAILY INTRACUTANEOUS INJECTIONS OF STAPHYLOCOCCAL VACCINE

As a preliminary step, the effects of the daily intracutaneous injections of the heat-killed staphylococcal vaccine were first observed in twelve guinea-pigs treated as follows:

On the first day, all of the guinea-pigs were given an intradermal injection of 0.2 cc. of the vaccine. All, except the one that was to be sacrificed twenty-four

23. Bloom, W.: Personal communication.
24. Maximow, A.: Ztschr. f. wissensch. Mikr. **26**:177, 1909.
25. Claudius, M.: Ann. Inst. Pasteur **11**:332, 1897.
26. Weigert, C.: Fortschr. d. Med. **5**:228, 1887.
27. Kockel: Centralbl. f. allg. Path. u. path. Anat. **10**:749, 1899.
28. Wolff, E.: Ztschr. f. wissensch. Mikr. **15**:310, 1898-1899.
29. Unna, P. G.: Monatschr. f. prakt. Dermat. **20**:140, 1895.
30. Schmidt, H.: Beitr. z. Anat., Physiol., Path. u. Therap. d. Ohres **27**:455, 1929.
31. Wallace, Helene M.: Science **74**:369, 1931.

hours later, were vaccinated in the right upper quadrant. In the latter the injection was made in the middle of the space between the umbilicus and the lower border of the sternum. This was done to study the same histologic structure in each animal, altered only by the effects of the vaccination. Twenty-four hours later the guinea-pig vaccinated in the center of the abdominal wall was killed after the area receiving the injection had been fixed on a cork frame. The same procedure was followed in the remaining animals in order to obtain ten specimens of skin that would demonstrate the progressive daily histologic changes occurring during the process of injections.

Gross Changes.—The gross changes occurring in the skin of normal guinea-pigs following the first injection of the staphylococcal vaccine were either the formation of a hyperemic nodule, varying from 2 to 10 mm. in diameter, and tending to become firmer and finally disappearing but leaving a pigmented macule, or the development of a nodule that softened, ulcerated, discharged a thick, yellow purulent material and then underwent rapid healing, leaving a slightly pigmented scar.

The subsequent injections usually produced larger nodules and produced them more rapidly, with more intensive reaction at the periphery and the base of the nodule. In many instances this reaction was so violent as to produce large areas of necrosis surrounded by elevated, hyperemic and edematous borders. The nodules of the previous injections were often reactivated to an inflammatory state by the later injections, as shown by the increased size of the area of hyperemia or by the formation of a necrotic area at the point of healing or in a quiescent nodule. In many guinea-pigs after the sixth injection a sudden rapid healing occurred in the previously elevated and hyperemic nodules, the discharge of some of the pustules disappeared and the entire skin was clean. In a few instances the violent local reaction after the fourth injection resembled grossly the Arthus phenomenon in the rabbit.

Histologic Changes.—The first injection of vaccine produced an inflammatory reaction characterized by dilatation of the lymphatics and blood vessels, edema, diapedesis of leukocytes, hemorrhage and moderate phagocytosis of the particles of vaccine by polymorphonuclear leukocytes and a small type of mononuclear cell. During the following injections, the inflammatory reaction was more intense, and there were signs of mobilization of the undifferentiated perivascular mesenchymal cells and of the connective tissue histiocytes and other reticular cells, with the appearance of numerous actively phagocytic mononuclear cells. In the first injection, the particles of vaccine were disseminated throughout the entire section, both extracellularly and in polymorphonuclear leukocytes. In the succeeding ones, the particles tended to localize within a relatively small area, which contained many polymorphonuclear leukocytes and was surrounded by many mesenchymal cells. After the second injection, the area of greatest reaction was that of the reticular and subreticular layers, with a moderate cellular infiltration in the papillary and muscular layers.

In the reticular and subreticular layers, the predominant cells during the first injection were the polymorphonuclear leukocytes, but in the subsequent ones mononuclear cells also appeared in great numbers. The polymorphonuclear leukocytes were vacuolated, many showed pyknosis and karyorrhexis, while others were digested or were in the process of being digested by small and large mononuclear cells and elongated histiocytes.

The final result of the injections was a definite increase in the thickness of the dermis with increased proliferation of mesenchymal cells as

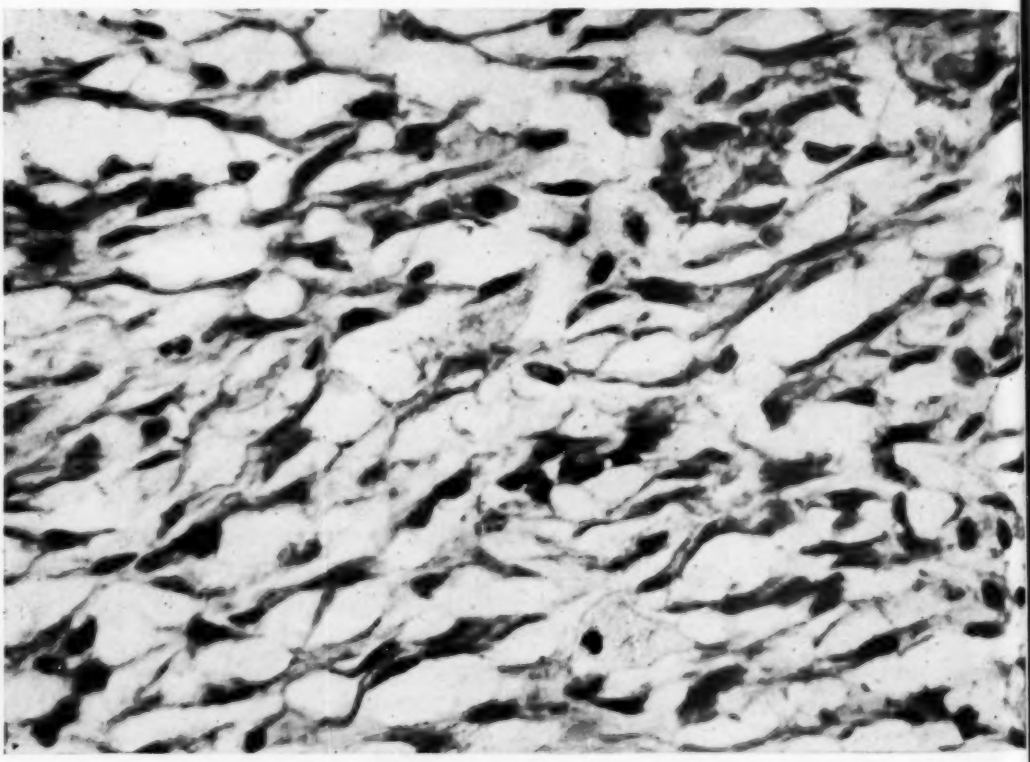

Fig. 1.—Photomicrograph (reduced from a magnification of × 700) of the subcutis of a guinea-pig after the tenth injection of the staphylococcal vaccine. Note the syncytium-like mass of mesenchymal tissue in which are many mitotic figures and some histiocytes with a foamlike cytoplasm.

manifested by the number of mitotic figures and infiltration by a great number of mesenchymal cells and leukocytes (fig. 1). The reticular and subreticular layers were greatly increased in thickness by innumerable quantities of mesenchymal and mononuclear cells, which were undergoing transformations resembling those seen in tissue cultures. There were rather numerous mitotic figures in the mesenchymal tissue and

pericytes of the blood vessels of the reticular, subreticular and muscular layers, and also a tendency toward the formation of a syncytium. Some of the mesenchymal cells were loaded with fat vacuoles. The polymorphonuclear leukocytes tended to disappear, leaving traces of their presence in the phagocytosed particles that were retained in the cytoplasm of the large mononuclear and histiocytic cells. The muscle layers were separated by a dense mesenchymal structure, which contained all the cell types of this tissue. The muscle bundles were separated by thick bundles of connective tissue. The blood vessels and lymphatics in most of the sections were dilated, patent and surrounded by many layers of undifferentiated pericytes, which frequently contained mitotic figures. In some instances the endothelial cells of the lymphatics and blood vessels were swollen. In the reticular and subreticular layers there was an increased number of new lymphatics and blood vessels. The entire thickness of the immunized skin was from three to ten times that of normal guinea-pigs.

GROSS CHANGES IN THE SKIN OF THE ABDOMINAL WALL IN GUINEA-PIGS AFTER INOCULATION OF LIVING, VIRULENT S. AUREUS

Normal Guinea-Pigs.—The gross changes produced in the skin and general health of normal guinea-pigs by the inoculation of 0.2 cc. of a living, virulent twenty-four hour agar culture of S. aureus were characterized, in general, by three types of reaction:

1. The formation in a few guinea-pigs of a small elevation of the skin with hyperemia and no further change during the entire period of observation.

2. The formation in some guinea-pigs of a hyperemic nodule which increased in size and density for from one to five days, until the surface became necrotic and opened to form a large, deep wound, which discharged pus and portions of the necrotic tissue for from twelve to sixteen days or more. Some of these guinea-pigs died before the wound was healed; in a few, secondary abscesses at the edges of the wound developed during the process of healing.

3. In others, an extensive cellulitis with the skin becoming purplish and edematous over nearly the entire anterior abdominal wall. The abdominal wall was cold, the guinea-pigs became extremely ill, and the majority of them died within from ten to forty-eight hours. From some of these, when the skin was cut at autopsy, much serosanguineous fluid escaped. The peritoneal surfaces were rough, with the fluid slightly turbid and increased in quantity, indicating peritonitis, presumably by extension from the area of cellulitis.

The gross effects in the twenty normal guinea-pigs inoculated with living staphylococci are summarized in table 1.

Guinea-Pigs Previously Given Intradermal Injections of Sterile Salt Solution.—The results obtained by the inoculation of 0.2 cc. of the living staphylococci into the guinea-pigs previously given intradermal injections of physiologic solution of sodium chloride were similar to those in the normal guinea-pigs, the gross effects being summarized in table 2.

It seems apparent, therefore, that repeated intradermal injections of salt solution did not modify in any significant way the reactivity of the tissues of the skin of the guinea-pigs to the subsequent injections of living staphylococci.

Guinea-Pigs Previously Given Local Injections of Staphylococcal Vaccine.—The results of the inoculation of the living staphylococci into

TABLE 1.—*Gross Effects on Normal Guinea-Pigs Inoculated Intradermally with Living S. Aureus*

Effect	Number	Percentage
Death within ten days	6	30
No change	2	10
Complete healing after sixteen days	1	5
Healing wound but covered by a crust after sixteen days	5	25
Open wound after sixteen days	6	30

TABLE 2.—*Gross Effects of Intradermal Inoculation of Living S. Aureus in Guinea-Pigs Previously Given Intradermal Injections of Physiologic Sodium Chloride*

Effect	Number	Percentage
Death within ten days	6	30
No change	1	5
Complete healing after sixteen days	1	5
Healing wound but covered by a crust after sixteen days	2	10
Open wound after sixteen days	10	50

the skin of guinea-pigs previously given local injections of the staphylococcal vaccine were as follows: In one guinea-pig a small, firm nodule appeared, which lasted for a few days and then gradually regressed. In others, small pustules developed, which discharged a thick, yellow purulent material and healed in from seven to fourteen days, leaving slightly pigmented scars. In most of the animals, however, nodules developed which increased in size and ulcerated after from three to five days, forming wounds that healed with small scars in fifteen days or less. It was apparent that these reacted quickly and effectively with rapid healing; furthermore, the death rate was one-half that of the normal guinea-pigs and that of the guinea-pigs previously inoculated with sterile physiologic solution of sodium chloride. The results for this group of twenty animals are summarized in table 3.

These experiments demonstrated that there is a great variability in the reactivity of the skin of normal guinea-pigs to the inoculation of living S. aureus. This may be explained by variation in natural immunity, which is more marked in some animals than in others. The results in the guinea-pigs given previous local injections of the staphylococcal vaccine indicated that the injection of killed staphylococcal vaccine had produced a change in the reactivity of the inoculated tissues to the extent of preserving the life of some guinea-pigs and of accelerating the healing process and restricting the dissemination of the bacteria in others.

TABLE 3.—*Gross Effects of Intradermal Inoculation of Living S. Aureus into Guinea-Pigs Previously Given Intradermal Injections of Staphylococcal Vaccine*

Effect	Number	Percentage
Death within ten days	3	15
No change	1	5
Complete healing after fourteen days	14	70
Healing wound but covered by a crust after sixteen days	1	5
Open wound after sixteen days	1	5

TABLE 4.—*End-Results of Inoculation of Living S. Aureus in Normal Guinea-Pigs and Those Previously Given Injections of Staphylococcal Vaccine from Which Inoculated Areas Were Excised*

Normal			Vaccinated		
	Number	Percentage		Number	Percentage
Dead	4	40	Dead	0	0
Healed in 13 days	1	10	Healed in 8 days	2	20
Healed in 14 days	2	20	Healed in 9 days	3	30
Healed in 19 days	3	30	Healed in 12 days	5	50

EFFECTS OF EXCISION OF THE AREA OF INOCULATION AFTER INTRADERMAL INJECTION OF LIVING STAPHYLOCOCCI

The rapidity of dissemination of living bacteria from the inoculated area was tested in another series of twenty guinea-pigs, ten of which were normal and ten of which had been previously treated locally with the staphylococcal vaccine. The guinea-pigs were paired according to weight, and the inoculations were performed five minutes apart. At intervals of one, two, three, five, seven, nine, twelve, fifteen, eighteen and twenty-four hours, a pair of animals was anesthetized, and from each a piece of tissue 10 by 10 by 2 mm. was excised around the point of inoculation. The wounds were closed with two or three stitches of silk no. 2, and the gross changes subsequently determined. Table 4 summarizes the after-effects. In the normal animals, healing was slow;

all the wounds opened within from one to four days, and there was a purulent discharge for more than sixteen days. The area where the silk stitches were placed became necrotic, and large pieces of greenish tissue sloughed off. The fatality rate in this series of animals was 40 per cent. The healing time was between thirteen and nineteen days, and in many guinea-pigs secondary abscesses developed in the neighborhood of the wound.

In contrast to these findings, the healing of the wounds in the guinea-pigs previously given injections of the staphylococcal vaccine was rapid, in some instances the wounds remaining closed and healing by first intention. In others, although the wounds opened completely, healing occurred within from eight to twelve days. Furthermore, no deaths occurred in these animals, and no abscesses recurred.

These experiments demonstrated that the bacteria in the skin of normal guinea-pigs disseminated quickly through the surrounding tissue, so that the excision of the infected area at one hour or at twenty-four hours did not prevent the fatal outcome or prevent delay in the healing processes. In the guinea-pigs previously given injections of the stapyhlococcal vaccine the bacteria were considerably localized, as demonstrated by the fact that the removal of the infected area protected the life of 40 per cent of these guinea-pigs, and shortened the period of healing of the wounds. Furthermore, the rapidity of healing of these tissues by primary union was striking, indicating that the harmful effects of the staphylococci had been largely eliminated.

HISTOLOGIC CHANGES AFTER INTRADERMAL INOCULATION OF LIVING S. AUREUS IN THE ABDOMINAL WALL IN GUINEA-PIGS

Similar experiments were next performed in order to study histologically at hourly intervals after the fifth hour the changes produced in the abdominal wall following the intradermal inoculation of 0.2 cc. of a living twenty-four hour agar culture of S. aureus. Sixty guinea-pigs were used, twenty normal, twenty previously given intradermal injections of the sterile salt solution, and twenty locally inoculated in the abdominal wall with the staphylococcal vaccine. From these three sets of guinea-pigs, groups of three of approximately equal weight (one from each set) were selected. In each group the individual inoculations of the living staphylococci were done five minutes apart in order to allow time to fix the tissues when they were later removed, and yet have similar hourly periods. After the fifth hour a group of three guinea-pigs was sacrificed each hour for the next twenty-four hours. By this procedure tissues showing hourly histologic changes following the inoculation of living staphylococci were obtained from twenty groups of guinea-pigs.

The general histologic changes occurring under these conditions have been described and illustrated in a previous paper (Cannon and

Pacheco), where the histologic differences in the normal and immunized animals were demonstrated. In the former, the characteristic picture was an extensive edema of the skin with dilatation of the blood vessels and lymphatics, hemorrhage and moderate infiltration by granular leukocytes and by a lesser number of small mononuclear cells. Histiocytes were inconspicuous, and there was no evidence of activation of the mesenchymal tissues. Some of the muscle bundles were undergoing hyaline degeneration. The blood vessels were dilated and engorged with blood, and at times contained many leukocytes that were in active stages

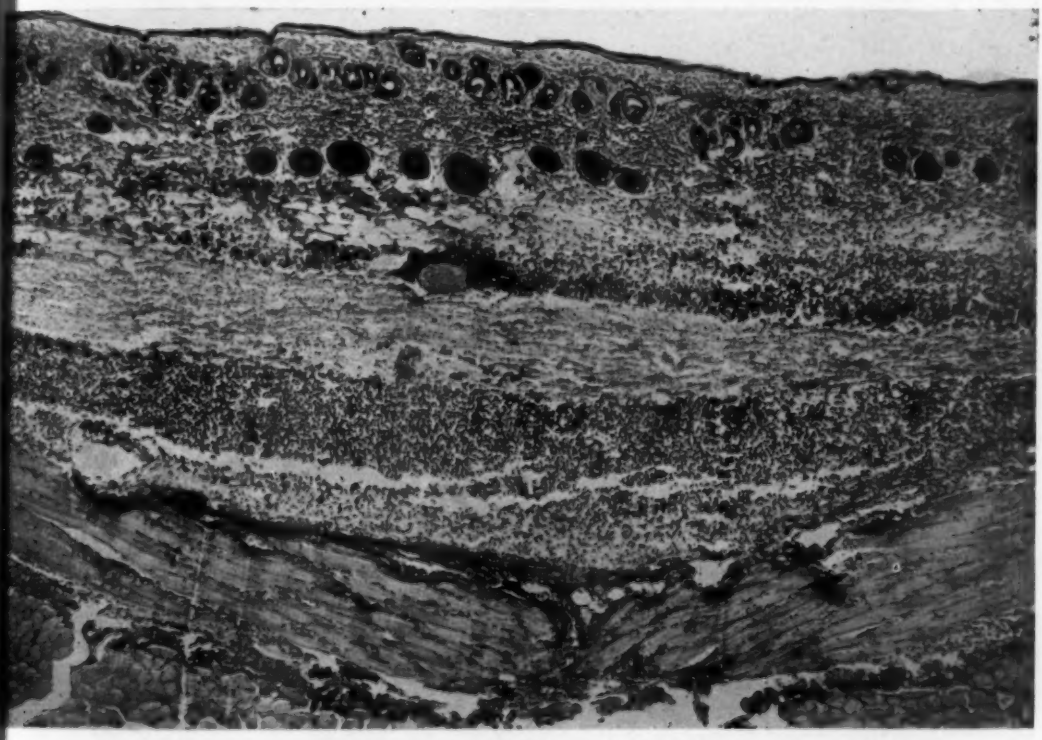

Fig. 2.—Photomicrograph (reduced from a magnification of × 70) of a section through the skin and entire abdominal wall of a normal guinea-pig inoculated with 0.2 cc. of a suspension of living, virulent S. aureus. The tissue was excised six hours after inoculation. The bacteria are disseminating through the reticulin or collagenic fibrils of the subreticular layer. There is a moderate cellular response, most of the cells being polymorphonuclear leukocytes, which contain many phagocytosed bacteria. The black area around the large venule consists of a concentrated mass of extracellular staphylococci, and the edematous layer of reticular fibrils beneath this contains large numbers of extracellular bacteria as shown in figure 3. The infection is obviously generalized, in spite of the abundant polymorphonuclear leukocytic response.

of diapedesis. The majority of the lymphatics were patent and dilated. No fibrin was found by the use of specific stains. The polymorphonuclear leukocytes showed innumerable bizarre figures, pyknosis, karyorrhexis and vacuoles. Enormous numbers of the polymorphonuclear leukocytes contained ingested staphylococci; many of the microorganisms were disseminated in long rows through the entire section, even extending into the connective tissue septums of the muscle layers. In many instances there were extensive areas of necrosis in the epi-

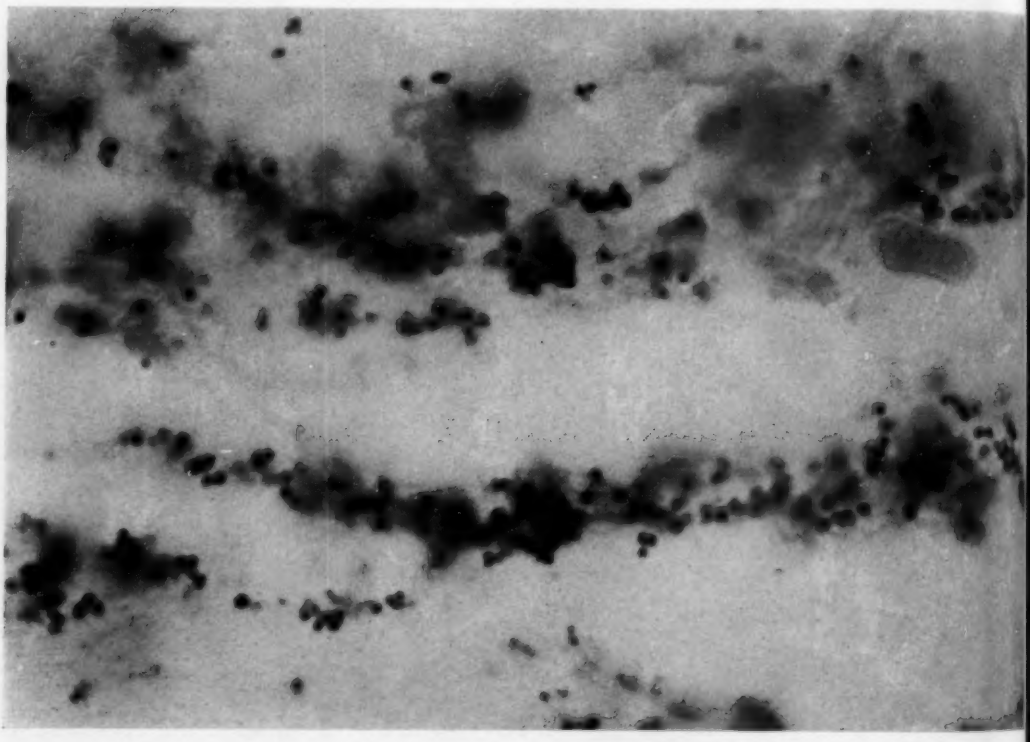

Fig. 3.—Photomicrograph (reduced from a magnification of × 2,650) of the section shown in figure 2. The bacteria are disseminating through the collagenic or reticulin fibrils. The cellular reaction is slight in this area. Note the absence of any agglomerative tendency of the bacteria.

dermis, papillary layers and muscularis. The subreticular layer was filled with polymorphonuclear leukocytes, eosin-stained precipitate and isolated groups or rows of free bacteria (fig. 2). The picture as a whole was that of an extensive cellulitis. It is noteworthy that in spite of widespread phagocytosis by the polymorphonuclear leukocytes the infection was disseminating widely.

The histologic changes in the skin of guinea-pigs previously given intradermal injections of normal salt solution were practically indistinguishable from those of the normal animals and will not be described in detail.

The histologic changes in the skin of guinea-pigs previously given local injections of the staphylococcal vaccine were characterized by a marked tendency to localization and clumping of the bacteria in a small area, which was filled with polymorphonuclear leukocytes, red blood

Fig. 4.—Photomicrograph (reduced from a magnification of × 70) of a section through the skin and a portion of the subreticular zone of a guinea-pig's abdominal wall previously immunized locally with the staphylococcal vaccine and later inoculated with 0.2 cc. of a living culture of S. aureus. Section taken six hours later. Note the localization of the bacteria in large masses in a small area, which is surrounded by a dense layer of mesenchymal cells. The area of polymorphonuclear infiltration and edema is very small. The black areas at the margins of the area of edema are masses of extracellular bacteria as shown in figure 5.

cells and small mononuclears (fig. 4). This localized area was in turn surrounded by large mononuclear leukocytes, histiocytes and many undifferentiated mesenchymal cells. As early as six hours, extracellular

masses of bacteria, as well as intensive phagocytosis by the small and large mononuclear and polymorphonuclear leukocytes, were noted. The polymorphonuclear response was intensive, but was localized largely to the area where the bacteria were fixed. Outside of the area, fewer polymorphonuclear leukocytes could be found between the mesenchymal tissues. The hemorrhage was also localized to the area where bacteria and the polymorphonuclear leukocytes were gathered, with the exception of two cases in which hemorrhage had occurred into the surrounding mes-

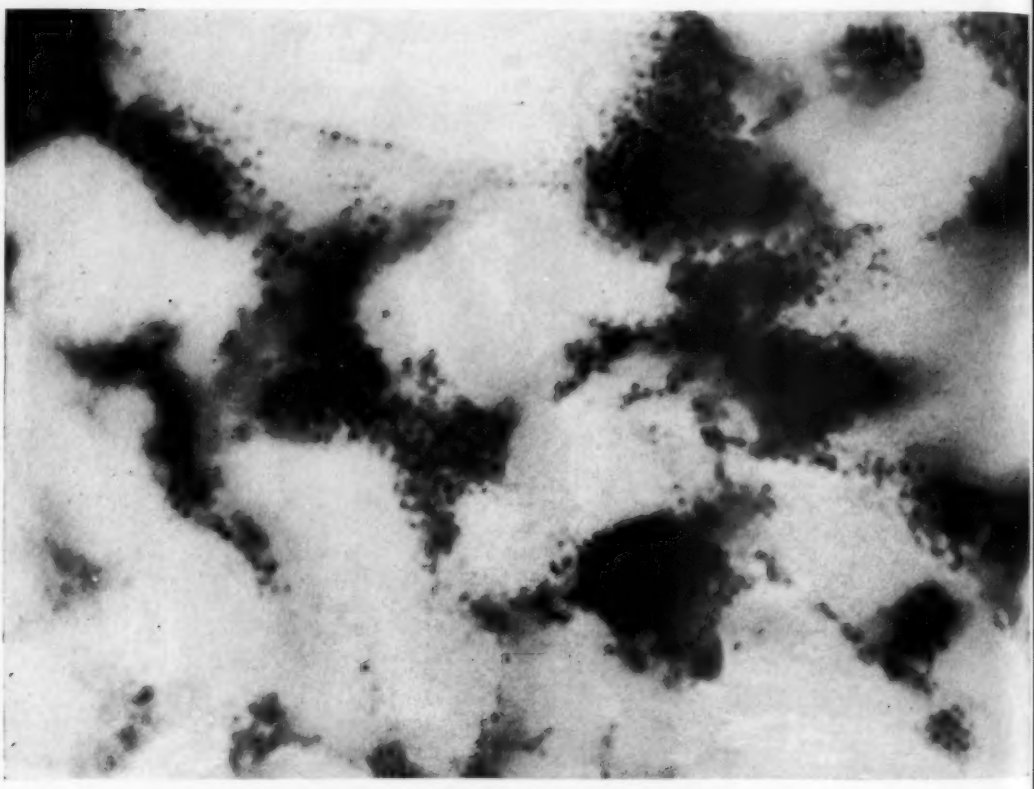

Fig. 5.—Photomicrograph (reduced from a magnification of × 2,650) of the section shown in figure 4 in an area where the bacteria are less concentrated. The bacteria are in masses. In many places the outlines of the bacteria cannot be made out.

enchymal tissue and the muscle layers. From the fifth to the twenty-fourth hour the polymorphonuclear leukocytes showed numerous bizarre shapes, were poorly stained, were vacuolated and showed evidences of degenerative changes. The mononuclear cells surrounding the polymorphonuclear leukocytes were in active stages of phagocytosis, as shown by the numbers of bacteria and polymorphonuclear leukocytes within their cytoplasm.

The bacteria as a whole were localized in large clumps to a small area as early as six hours after the inoculation (fig. 5), and after twelve hours most of them were intracellular. Both intracellular and extracellular injury of bacteria was indicated by their swollen and poorly stained appearance.

In the remainder of the reticular and subreticular layers there were several rows of connective tissue cells, many of which were proliferating, as shown by numerous mitotic figures. The area of localization was, as a rule, in the reticular and subreticular layers, although in a few cases the bacteria were localized in the papillary layer. In others there was a local necrosis of the epithelium and papillary layers. The papillary and muscular layers contained local phagocytic cells of many bizarre shapes, as though they had been fixed while in an active stage of ameboid movement, but very little necrosis was noted in these layers. The blood vessels and lymphatics were largely patent, and in many instances there were many patent new small blood vessels in the mesenchymal tissue of the subreticular layer. After a thorough search few thrombosed blood vessels or lymphatics were found; on the other hand, many of these structures seemed to be dilated. Fibrin could not be found with specific stains, and with hematoxylin and eosin the picture was that of a compact mass of bacteria, polymorphonuclear leukocytes and mononuclear cells, surrounded by a dense mass of mesenchymal tissue in which Mallory's connective tissue stain revealed a network of reticulin and collagenic fibrils in the reticular and subreticular layers.

COMMENT

These experiments demonstrate that living virulent staphylococci may be effectively localized in the cutaneous tissues of guinea-pigs previously given injections in the same area of a heat-killed suspension of S. aureus. This vaccination leads to the development of a locally superior mechanism for the disposal of living staphylococci when they are injected later. The experiments, however, do not differentiate between the effects of local and general resistance. Data concerning that problem will be presented in a later paper.

The specific purpose of this work was to study in detail the morphologic changes induced in the mesenchymal tissue by the injection of a staphylococcal vaccine, and to determine to what extent these changes altered the normal reactivity to a living, virulent suspension of S. aureus. Consequently, serologic studies of the blood serum and local tissues were not made.

It is apparent that the intradermal injection of heat-killed staphylococci called forth a pronounced cellular response in the skin of the anterior abdominal wall of guinea-pigs. This response was predominantly of polymorphonuclear leukocytes, followed shortly by mobilization

and proliferation of mononuclear cells. The latter arose *in situ* to a large extent, as shown by the numerous mitotic figures, but many also entered from the blood stream. By the fourth day these mononuclears were actively phagocytic and contained in their cytoplasm particles of vaccine and polymorphonuclear leukocytes in various stages of disintegration. By the tenth day of the inoculations the dermis was from three to ten times the thickness of that in normal animals. The reticular and subreticular layers looked like a syncytium, in which were many new blood vessels and lymphatics. The picture in general resembled that described by Gay, Clark and Linton [32] in the pleural and peritoneal wall of rabbits into which nonspecific irritants, such as aleuronat-starch mixtures, had been injected.

The inoculation of living, virulent staphylococci into the abdominal wall of guinea-pigs previously treated with the staphylococcal vaccine was followed by a distinctly different response from that of normal guinea-pigs, as measured by the degree of illness, the fatality rate, the ability of the tissues to heal, the histologic reaction and the degree of phagocytosis. The degree of illness was never as pronounced in the previously treated guinea-pigs as in the normal ones. The fatality rate was one-half that of the normal guinea-pigs, and the ability of the tissues to heal after an area of necrosis was produced or after the excision of the area inoculated was surprisingly rapid and without complications. The histologic reaction was characterized by a localization of the staphylococci in clumps, usually in a small area of the subreticular layer, although in two instances this localization took place in the papillary layer. The epithelial covering of the area of localized cocci usually became necrotic. The central portion of the cellular reaction consisted of polymorphonuclear leukocytes and a few mononuclear cells. These polymorphonuclear and mononuclear phagocytes in turn were localized by innumerable mesenchymal cells of the local tissues. The phagocytic activity of the cells was marked, as evidenced by the great number of cocci within a single phagocyte.

The mechanism of localization of such large numbers of virulent staphylococci within a small area of skin of a locally treated guinea-pig as contrasted with their widespread dissemination in the skin of a normal guinea-pig, is obviously of great significance. Various ideas have been advanced to explain this mechanism. Cobbett and Melsome [9] thought that it was the result of an early inflammatory reaction, which destroyed the micro-organisms before they had time to adjust themselves to the new environment, to proliferate and to liberate their toxins. Wassermann and Citron [33] postulated the idea of "Umstimmung," or retuning,

32. Gay, F. P.; Clark, A. R., and Linton, R. W.: Arch. Path. **1**:857, 1926.

33. Wassermann, A., and Citron, J.: Deutsche med. Wchnschr. **31**:573, 1905.

of the cells of the area which had been sensitized. Noguchi [11] mentioned the possibility of a local formation of antibodies in the connective tissue of the areas previously in contact with a bacterial antigen. Opie [34] demonstrated the fixation of an antigen at the site of inoculation in tissues sensitized to that antigen. His explanation of such a phenomenon was based on the assumption of the local occurrence of an anaphylactic inflammation.

Menkin [35] recently advanced the idea that bacteria and particulate matter are fixed in an area previously inflamed because of the barrier action of thrombosed lymphatics and the deposition of fibrin. This explanation, however, seems inadequate in the present series of experiments, first, because the sections show many more patent than thrombosed blood vessels and lymphatics, and secondly, because of a complete absence of fibrin as revealed by the use of specific staining methods. Although there is a semblance of fibrin in sections of the skin of normal guinea-pigs inoculated with staphylococci and stained with hematoxylin and eosin, such is not the case in sections of the skin of guinea-pigs previously treated with the staphylococcal vaccine. Furthermore the use of nine specific stains for fibrin has failed in every instance to demonstrate its presence.

The countless numbers of phagocytes may act as a mechanical barrier, especially in cases of nonspecific immunity, but in specific immunity the local presence of immune bodies must be taken into consideration. It is probable that the general mechanism of fixation is as follows: The vaccine introduced intradermally is retained and metabolized principally by the local phagocytes, with the resulting formation of antibodies which in turn tend to fix the antigen at the site of inoculation by a precipitating reaction, as Opie [4] demonstrated, or else the union of antigen with antibody produces a physicochemical change in the tissues that hinders dissemination of the antigen from the area. Evidence for the presence of agglomerating or flocculating antibodies is furnished by the morphologic demonstration of agglutination in vivo, as reported in a previous paper by Cannon and Pacheco.[36] Further evidence of the presence of local antibodies is suggested by the great degree of swelling of the bacteria injected into the locally treated tissues and by the vigorous phagocytosis by the microphages and macrophages. Similar observations were made by Bordet [37] and Tsuda.[38] More recently, Cannon and Sullivan [39] demonstrated by methods of chemical extraction that anti-

34. Opie, E. L.: J. Immunol. **9**:255, 1924.

35. Menkin, V.: J. Exper. Med. **53**:171, 1931.

36. Cannon, P. R., and Pacheco, G. A.: Am. J. Path. **6**:749, 1930.

37. Bordet, J.: Ann. Soc. roy. d. sc. méd. et nat. de Brux. **4**:455, 1895.

38. Tsuda, S.: Virchows Arch. f. path. Anat. **247**:121, 1923.

39. Cannon, P. R., and Sullivan, F. L.: Proc. Soc. Exper. Biol. & Med. **29**:517, 1932.

bodies may be formed locally in an area of local immunization and may persist there in greater concentration than elsewhere, as, for instance, in adjacent unimmunized skin, blood serum, spleen and liver. These findings strengthen the view that local formation and concentration of antibodies may play an important part in the mechanism of local immunity. The "Umstimmung," or retuning, as suggested by Wassermann and Citron [33] may thus be explained as due to the local concentration of immune bodies formed by locally mobilized mesenchymal cells, the latter having elaborated the immune bodies during the period of local immunization. The introduction of antigen into a tissue containing locally a high concentration of specific antibodies between and probably on the surfaces of histiocytes may lead to an antigen-antibody reaction tending to localize the antigen immediately. Secondary to this union, the vasomotor reactions and leukocytic infiltration tend further to keep the antigen fixed, thus preventing the harmful effects of its generalization.

CONCLUSIONS

The continued local intradermal treatment of guinea-pigs with a heat-killed suspension of S. aureus leads to the proliferation and mobilization of large numbers of macrophages in the area treated.

The subsequent inoculation into such an area of living, virulent staphylococci is followed by an accelerated inflammatory response and healing, with localization of the bacteria in the area inoculated.

The localization is due primarily to an antigen-antibody reaction whereby the bacteria tend to become agglomerated and presumably opsonized, and then engulfed by phagocytes, both microphages and macrophages.

This localization does not seem to be significantly influenced by such mechanical barriers as a deposition of fibrin or thrombosis of lymphatics and blood vessels.

As a result of these local tissue changes the harmful effects of the generalization of the bacteria are to a great extent prevented.

THE STEM CELL OF THE MONOCYTE

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In a recent communication,[1] I described a method of silver impregnation of blood cells spread on cover glass films that, owing probably to dissociation, concentration and partial loss of hemoglobin, revealed an unusual and probably artificial structure in the erythrocyte and gave unusually sharp details of the nuclei of white blood cells. It is believed that considerably more precision in outlining chromatin is achieved with this than with the usual technical procedures.

With this method at hand, a case of monocytic leukemia gave an opportunity to study the nuclear structure of the monocyte in detail.[2] The case was of particular value for this type of study, as the cells in the circulating blood belonged almost exclusively to the monocytic series, and at certain periods of the illness cells at all stages of development were present. A brief outline of the history of the case follows:

A white man, aged 30, who was a poultry expert, entered the hospital with the complaints of weakness, soreness of the gums and painful swelling in the left side of his neck and face. He had noticed undue fatigability for one and one-half years, which had become more severe during the past few weeks. Two weeks before he entered the hospital, his gums had become sore, and the lower teeth had become loose. Following this, sore throat and the painful swelling in the left side of the neck had developed.

Physical examination revealed a pale young man with a swelling at the left side of the face and neck and small purpuric spots scattered over the trunk and lower extremities. The gums were soft and discolored, with a small area of ulceration at the margin. The tonsils were enlarged and reddened. There were moderately enlarged lymph nodes in the submental and upper cervical regions, and several nodes from 2 to 3 cm. in diameter in both axillae. The inguinal nodes were small. The edge of the spleen was felt 4 cm. below the costal margin.

In spite of repeated transfusions of blood and other therapeutic measures, the course of the illness was rapidly unfavorable, with death eighteen days after entry.

Submitted for publication, Jan. 30, 1932.

From the Thorndike Memorial Laboratory and the Second and Fourth Medical Services (Harvard) of the Boston City Hospital, and the Cancer Commission of Harvard University.

1. Rinehart, J. F.: Unusual Structures in the Erythrocyte: II. A Precise Nuclear Impregnation Method, Anat. Rec. **52**:151, 1932.

2. Dr. George R. Minot and Dr. Claude E. Forkner gave me permission to study the blood in this case.

The majority of the cells in the blood throughout the course of the illness were monocytes, typical in reaction in supravitally stained and Wright-stained preparations.

All of the differential counts of white blood cells given in the following paragraphs were made from supravitally stained preparations by an independent observer experienced in the use of this method.[3]

The blood on entry showed: red blood cells, 2,190,000 per cubic millimeter; hemoglobin, 8 Gm. per hundred cubic centimeters; white blood cells, 62,000 per cubic millimeter, with the following differential count—mature monocytes, 76.5 per cent; young monocytes, 12.5 per cent; monoblasts, 5 per cent; polymorphonuclear neutrophils, 0.5 per cent; polymorphonuclear basophils, 0.5 per cent; myelocytes, 0.5 per cent, and small lymphocytes, 4.5 per cent.

During the course of the illness, the total number of white blood cells ranged from 34,000 to 150,000 per cubic millimeter, with mature monocytes ranging in number from 72 to 96 per cent, young monocytes from 2 to 20 per cent and monoblasts from 1 to 5 per cent. Histiocytes (macrophages) were not seen.

BRIEF REVIEW OF THE LITERATURE ON THE HEMOHISTIOBLAST

Because of its important rôle in this study, I shall briefly review the history and present status of the cell known as the hemohistioblast or the Ferrata cell. While no attempt is made to review completely the extensive literature bearing on the cell, reference is made to representative pertinent data.

Franco and Ferrata,[4] in 1919, described in the peripheral blood and spleens of patients with chronic myelogenous leukemia, a cell of distinctive morphologic character that had not been previously recognized. Subsequently, Ferrata [5] and others advanced a convincing number of data supporting the separate identity of this cell, which Ferrata called the hemohistioblast. This investigator identified the cell chiefly by the unique character of its nucleus, which he likened to a sponge. The cytoplasmic outline is usually irregular and frequently shows pseudopedia. Ferrata's conception of this cell is briefly as follows: It is the stem cell from which the monocyte and the lymphocyte arise, and from which cells of the granulocytic series may be derived without passing through the myeloblastic stage. The cells are divided into three categories as follows: (1) cells without granules, (2) cells with azure granules or filaments and (3) cells with specific neutrophilic or eosinophilic granules. In the cells of the first two groups, from one to several nucleoli are present.

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3. The differential counts were made by Dr. C. E. Forkner. He also permitted me to use his records and gave other help in this study. A more detailed report of this case will be made by Dr. Forkner at a later date. Miss Charlotte Clarke and Miss Rose Hermann prepared the excellent cover glass blood films used in this study.

4. Franco, E., and Ferrata, A.: Arch. per le sc. med. **43**:109, 1919.

5. Ferrata, A.: Haematologica **2**:242, 1921; **5**:228, 1924.

Gasbarrini [6] noted the presence of the hemohistioblast in lymphatic leukemia. Reitano [7] recorded observations on the hemohistioblast in monocytic leukemia. Di Guglielmo [8] presented evidence that the primitive cell of the circulating blood in the embryo in the prehepatic period of the formation of the blood was the hemohistioblast. Esposito [9] confirmed Ferrata's observations on this cell in five cases of myelogenous leukemia and observed a similar cell in three cases of lymphatic leukemia. Massazza [10] recorded the presence of the hemohistioblast in the blood of a patient with severe anemia during pregnancy. De Souza Aranha [11] observed, in the blood of a person with malaria and syphilis, true hemohistioblasts of the type recorded for leukemia, coincident with monocytosis. Richter [12] reported observations on the hemohistioblast in four cases of myelogenous leukemia, one case of lymphatic leukemia and one case each of malaria, staphylococcus septicemia and von Jaksch's anemia. Fontana,[13] in a study of an unusual clinical syndrome described as "mielosi eritremica pseudo-aplastica," placed the hemohistioblast as the precursor of the megaloblast.

The identity of the cell has, however, been contested by several hematologists. Naegeli,[14] Ringoen,[15] Lambin [16] and Fegler [17] considered the cell to represent damaged forms of the usual circulating elements. Lambin and Ringoen offered as a serious argument against the identity of the cell the failure to see the cell in vitally stained preparations. I do not consider this a valid argument for the following reason: The hemohistioblast is recognized chiefly by its peculiar open, lacelike or spongelike nucleus, and the supravital preparation is of little value in studying the minutiae of the internal architecture of the nucleus. Further, in cases of leukemia there are cells, particularly the more primitive forms, that cannot be identified by even the most experienced observer. There are, of course, damaged cells in almost any preparation of blood containing many young white blood cells. Some of these broken cells have a certain resemblance to the hemohistioblast, but I believe that this resemblance is superficial. The hemohistioblast presents

6. Gasbarrini, A.: Haematologica **1**:260, 1920.
7. Reitano, D.: Haematologica **3**:524, 1922.
8. di Guglielmo, G.: Haematologica **3**:469, 1922.
9. Esposito, A.: Haematologica **4**:269, 1923.
10. Massazza, M.: Haematologica **6**:94, 1925.
11. de Souza Aranha, M. E.: Haematologica **6**:328, 1925.
12. Richter, M. N.: Am. J. M. Sc. **169**:336, 1925.
13. Fontana, A.: Haematologica **10**:303, 1929.
14. Naegeli, O.: Blutkrankheiten und Blutdiagnostik, ed. 4, Berlin, Julius Springer, 1923.
15. Ringoen, A. R.: Folia haemat. **33**:149, 1927.
16. Lambin, Paul: Haematologica **8**:1, 1927.
17. Fegler, G.: Compt. rend. Soc. de biol. **96**:347, 1927.

a nuclear structure too delicate and too clearly delineated to be considered a damaged element. A further objection of Lambin and Ringoen to the identity of the cell is the fact that it does not resemble, in nuclear structure, the resting cell of the reticulo-endothelium or its derivative, the phagocytic histiocyte (macrophage). Ferrata recognized this. I agree that the histiocyte and the hemohistioblast present different nuclear patterns. The histiocyte possesses a distinctly denser, more closely knit chromatin than the hemohistioblast. (Contrast the histiocyte in figure 1 with the hemohistioblasts in figures 2 and 3). Ferrata considered, however, that the hemohistioblast is derived from the reticulo-endothelium, and that the transformation to a cell with the spongy-

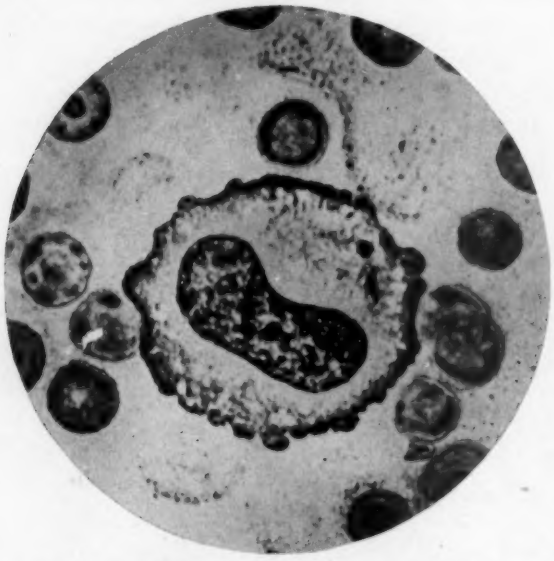

Fig. 1.—A macrophage (histiocyte) showing the relatively dense, closely drawn nucleus and the large amount of cytoplasm that are characteristic of this cell. The cytoplasm contains a phagocytosed fragment of an erythrocyte. Note that this cell differs in nuclear character from the hemohistioblast. Photomicrograph; × 1,750.

appearing nucleus is a morphologic expression of the mobilization of the cell. I believe it is probable that, under a stimulus causing active proliferation of the cells of the reticuloendothelium, they assume a nuclear form of more primitive type with a looser organization of chromatin. This opinion finds support in the observations of Merklen and Wolf on the pathologic changes in monocytic leukemia, in which they found the essential abnormality to be a proliferation of the specific or reticulo-endothelium. They described an enlargement of the reticulum cells with "brightening" of the nucleus and loosening of the chromatin into a fine network.

One observation by Ferrata [8] of fundamental significance and apparently frequently overlooked is that a close similarity in nuclear pattern obtains between the hemohistioblast and the cell of the embryonic mesenchyme. It is generally considered that in the adult organism cells exist that are of mesenchymal type of potentiality. It would not, then, seem unusual in the presence of a stimulus, as in leukemia, occasioning active proliferation of mesenchymal cells or of a tissue little differentiated from the mesenchyme, as the reticulo-endothelium, to have cells of mesenchymal form produced and appearing in the circulating blood. While one may object, perhaps, to the complete thesis

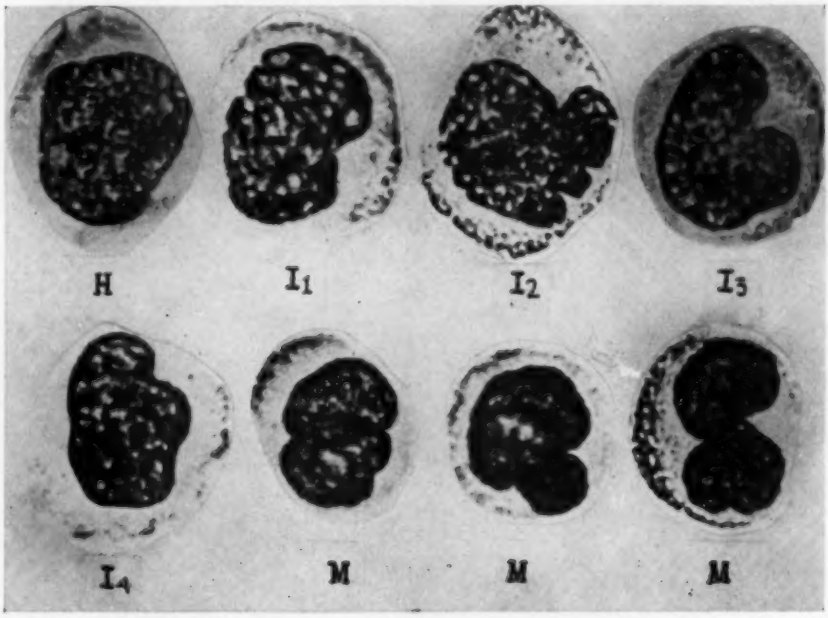

Fig. 2.—Cells selected from a single blood film in a case of monocytic leukemia illustrating the spongelike nuclear character of the hemohistioblast (H) and showing intermediate stages of differentiation (I_1 to I_4) into the mature monocytes (M). Photomicrograph; × 1,750.

of Ferrata, there appears to be a strong chain of evidence supporting the separate identity and great potentialities of this cell. To recapitulate, the hemohistioblast is found almost consistently in myelogenous leukemia and has been described in lymphatic leukemia and in monocytic leukemia; the cell has been shown to be the circulating stem cell in the prehepatic period of the formation of the blood in the embryo, and the megaloblast has been traced to the same cell. Further, the cell, as Ferrata pointed out, corresponds in nuclear type to the mesenchymal cell, the logical form of a multipotential element.

It is the purpose of the subsequent section to trace the nuclear development of the monocyte from a cell of this type in monocytic leukemia.

In this study, there was observed a small but definite number of cells corresponding in nuclear architecture to the hemohistioblast. Further, many cells were seen with a nuclear structure intermediate in

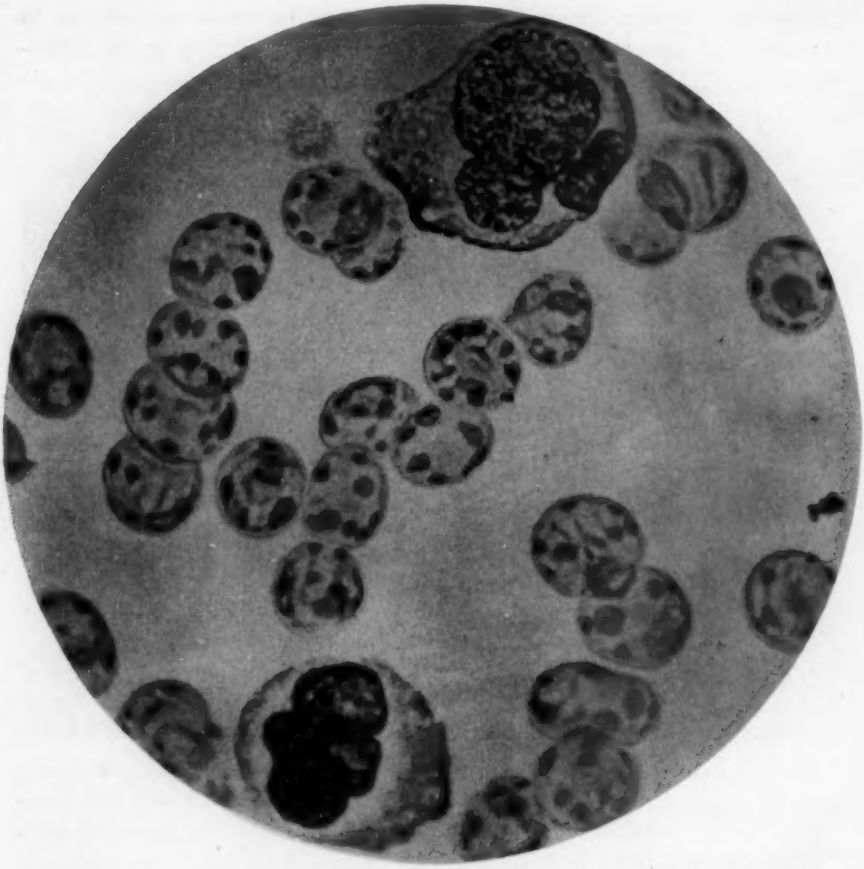

Fig. 3.—The cell above shows the typical spongelike nuclear character of the hemohistioblast, and the cell below, the softly drawn, skeinlike nucleus of the mature monocyte. Photomicrograph; × 1,750.

form between the hemohistioblast and the monocyte. It has been possible, from a single blood film, to select a series of cells showing a gradual transformation of the nuclear structure from that of the hemohistioblast to that of the mature monocyte (fig. 2).

A brief description of the nuclear architecture in the various forms, as revealed by my technic, is given in the following paragraphs.

DEVELOPMENT OF THE MONOCYTE FROM THE HEMOHISTIOBLAST

The Hemohistioblast.—In dry fixed films stained by the silver impregnation method, the nucleus of the hemohistioblast presents a net-like structure. The interlacing of the fine, but clearly separated, chromatin filaments produces a delicate lacelike pattern. From two to five small, round or oval nucleoli are usually visible in addition to the tiny open spaces between the lines of chromatin. The cytoplasmic outlines frequently are indistinct and may be quite irregular. Figure 3 shows a hemohistioblast with this characteristic architecture, accompanied by an adult monocyte. The hemohistioblast shown in figure 3 has features that make the supposition that it is a traumatized cell very unlikely. The nucleus maintains its normal rounded contour, and an unusual accessory lobule is undisturbed. Further evidence against trauma causing the appearance of hemohistioblasts is the fact that in traumatized portions of films the injured monocytes were recognized as such and did not show the nuclear structure of the hemohistioblast or the intermediate forms to be described. The cell *H* in figure 2 again illustrates the characteristic nuclear pattern of the hemohistioblast.

Intermediate Forms.—Cells intermediate in nuclear form between the hemohistioblast and the monocyte are best described by reference to figure 2. It will be seen that the intermediate forms, while retaining to some degree the spongelike nuclear character of the hemohistioblast, show thickening and apparent fusion of the filaments of chromatin, accompanied by indentation of the nucleus as the adult type of cell is approached. See figure 2 I_1 to I_4.

The Mature Monocyte.—The majority of the cells present were mature monocytes. The mature monocyte stained by the silver impregnation method presents an aspect quite characteristic and is rather clearly differentiated from the other leukocytes. The chromatin presents a moderately dense, but dull, softly drawn appearance, different from the denser, more uniform chromatin of the lymphocyte, and the brighter, heavy lines or blocks of chromatin in the myelocyte. The nuclei, of course, show the characteristic foldings, producing a series of true or bizarre kidney shapes. The nuclear character of the mature monocyte is illustrated in figures 2 *M* and 3.

(Contrast the mature monocytes with the myeloid elements shown in figure 4.)

Wright-Stained Blood Films.—Study of the Wright-stained blood films revealed essentially the same nuclear characters, although these lacked the sharp contrast of outlines achieved by the silver impregnation method. The majority of the Wright-stained cells showed the appearance of typical monocytes, with indented or folded nuclei and faintly basophilic cytoplasm stippled with fine, azure granules and rods. The

cytoplasm stained a dull grayish blue and presented faintly stained azure granules and filaments. Rarely a cell with the hemohistioblastic sponge-like nucleus was seen, with eosinophilic granules. Practically all of the cells of the monocyte series showed azure granules or filaments in the cytoplasm.

ASSOCIATION OF THE MONOCYTE AND HEMOHISTIOBLAST

The association of the monocyte and hemohistioblast in the circulating blood in various pathologic conditions has been observed by a number of investigators. Ferrata and Negreiros-Rinaldi[18] noted the association of the hemohistioblast and the monocyte in malaria. Some of the cells

Fig. 4.—A group of cells in a case of myelogenous leukemia including a myeloblast, two myelocytes, a young eosinophilic polymorphonuclear leukocyte and a neutrophilic polymorphonuclear leukocyte. Note that the chromatin is coarser and denser in the myelocytes than in the monocytes illustrated in the other figures. Photomicrograph; × 1,750.

described by these authors were, however, undoubtedly macrophages. De Souza Aranha[11] observed, in the blood of a person with malaria and syphilis, true hemohistioblasts of a type identical with that of the hemohistioblasts in leukemia accompanying monocytosis. Richter[12] observed what he characterized as monocytoid hemohistioblasts in cases of quartan malaria and staphylcoccus septicemia, and considered that all stages from the hemohistioblast to the monocyte were present. Many of the cells described by him were, however, phagocytic, and it is probable that some of the cells he observed were macrophages (histiocytes).

18. Ferrata, A., and Negreiros-Rinaldi: Haematologica **1**:243, 1920.

Although Dameshek [19] failed to draw a line of distinction between the hemohistioblast of Ferrata and the macrophage, he undoubtedly observed the association of the hemohistioblast with the monocyte in monocytic leukemia. He noted specifically the presence of the hemohistioblast with the "spongy" nucleus in two cases of monocytic leukemia.

Reitano,[7] as previously noted, reported the presence of the hemohistioblast in monocytic leukemia and considered the monocyte to be derived from this cell, without, however, describing intermediate phases of differentiation. This author described the hemohistioblast in myelogenous leukemia as appearing in the different types, i. e., without granules, with azure granules, and with neutrophilic or eosinophilic granules.

Merklen and Wolf,[20] in a rather extensive study of the subject of monocytic leukemia, reported a case in which there were 20,500 white blood cells per cubic millimeter with 71 per cent monocytes or monoblasts, 14 per cent cells of the Ferrata type (hemohistioblasts), 14 per cent lymphocytes and 1 per cent myelocytes. These authors expressed the opinion that the Ferrata cells probably represented fragile monoblasts. Forkner [21] showed that the so-called monoblast is closely related to the undifferentiated mesenchymal cell. It would seem more probable that the Ferrata cells seen by Merklen and Wolf represented an earlier stage than the monoblast, or true mesenchymal cells. Ferrata [5] called attention to the similarity in nuclear architecture of the hemohistioblast and the mesenchymal cell. This frequently recorded association of hemohistioblast and monocyte cannot be considered mere chance, and the logical conclusion would be that they are genetically related.

COMMENT

The origin of the monocyte has been assigned variously to the myeloblast, the common or the specific endothelium, the lymphocyte and an undifferentiated mesenchymal cell.

Naegeli [14] considered the cell a member of the myeloid series arising from the myeloblast. McJunkin [22] and others expressed the belief that the monocyte is derived from common endothelium. Aschoff [23] and Kiyono [24] placed the monocyte in close relation with the specific endothelium (reticulo-endothelium) and its derivatives, the histiocytes

19. Dameshek, W.: Arch. Int. Med. **46**:718, 1930.
20. Merklen, P., and Wolf, M.: Rev. de méd. **45**:154, 1928; Arch. d. mal. du cœur **21**:129, 1928.
21. Forkner, C.: J. Exper. Med. **52**:3, 1930.
22. McJunkin, F.: Am. J. Anat. **25**:27, 1919.
23. Aschoff, L.: Verhandl. d. deutsch. path. Gesellsch. **16**:107, 1913.
24. Kiyono, K.: Die Vital Karminspeicherung, Jena, Gustav Fischer, 1914.

or macrophages. Bloom [25] considered the monocyte to arise through intravascular transformation of the small lymphocyte. Maximow,[26] too, believed an origin from the lymphocyte to be most probable, but admitted the possibility of an origin from the histiocyte or from an undifferentiated mesenchymal cell.

Cunningham, Sabin and Doan [27] described an origin of the monocyte from a primitive blood cell that itself is closely related to undifferentiated mesenchymal elements in the hematopoietic organs. Forkner [21] made a careful study of the origin of monocytes in the peripheral lymph nodes of the normal rabbit, and concluded that they arose from primitive, undifferentiated mesenchymal cells, passing through a stage which he calls a premonocyte, into the monocyte. He found no evidence that they arose under normal conditions from the macrophage (histiocyte) or from the reticulo-endothelium. He, like Simpson,[28] did, however, consider that the monocyte might be transformed into a macrophage. Forkner failed to find any evidence that the monocyte arose from the myeloblast, confirming the previous observations of Sabin and Doan.[29]

This study, tracing the development of the nucleus of the monocyte from a stem cell corresponding in nuclear architecture to the hemohistioblast, would appear to strengthen the position of the hemohistioblast as a true stem cell. Accepting the observation of Ferrata [5] that the hemohistioblast corresponds to the cell of the embryonic mesenchyme, this study consequently would favor the view held by Cunningham, Sabin and Doan [27] and Forkner [21] that the precursor of the monocyte is an undifferentiated mesenchymal cell. The observations recorded, of course, do not define the limits of the tissues from which cells of mesenchymal type may arise. They do not preclude the possibility of the reticulo-endothelium, under the stimulus of proliferation, being this source. Indeed, the observations of Merklen and Wolf, previously cited, would favor this view.

SUMMARY

By application of a silver impregnation method of staining to blood films in a case of monocytic leukemia, the monocyte has been traced to a stem cell corresponding to the hemohistioblast of Ferrata. A graded series of intermediate forms exists between the round or oval, lacelike nucleus characteristic of the hemohistioblast and the folded, skeinlike nucleus of the mature monocyte.

Miss Adelaide M. Hayes prepared the photomicrographs used in this article.

25. Bloom, W.: Folia haemat. **37**:1, 1928.

26. Maximow, A.: Arch. Path. **4**:4, 1927.

27. Cunningham, R. S.; Sabin, F. R., and Doan, C. A.: The Development of Leucocytes, Lymphocytes and Monocytes from a Specific Stem Cell in Adult Tissues, Washington, D. C., Carnegie Institution, 1925, publication no. 361, p. 227.

28. Simpson, M.: J. M. Research **43**:77, 1922.

29. Sabin, F. R., and Doan, C. A.: Proc. Soc. Exper. Biol. & Med. **25**:121, 1927.

EXPERIMENTAL ABSCESSES IN THE RABBIT

CYTOLOGY AND DRAINAGE

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Experimental abscesses are easily produced in man, and they are frequently produced for therapeutic purposes by the subcutaneous administration of turpentine. In animals, however, such abscesses are less easily produced. Hohnfeldt [1] produced them by the injection of a culture of staphylococci in an emulsion of agar, and Kiyono [2] inserted small pieces of sponges soaked either in a culture of staphylococci or in turpentine intramuscularly to produce pyogenic membranes. The literature on the cytology of these inflammatory reactions is enormous, and I shall not attempt to review it. The reader is referred to the excellent reports by Sabin [3] and by Maximow.[4]

Although the cytologic reaction in a given field of inflammation is generally well known, fewer data are available concerning absorption from such lesions. It is generally known that the absorption of a crystalloid or true solution takes place by way of the blood stream, but that the absorption of colloid solutions or suspensions of particulate materials is a function of the lymphatic radicles. It is probably true that absorption from an inflammatory region differs considerably from the normal, in that there are periods when complete occlusion of either lymphatic or venous radicles occurs. Rokitansky [5] maintained that absorption and inflammation are incompatible, and that inflammation must subside before any absorption from an inflammatory region can take place.

This study was undertaken to determine the extent and rate of absorption of both crystalloid and colloid solutions from experimental abscesses at varying intervals after their development.

Submitted for publication, Feb. 11, 1932.

Work done in the Division of Experimental Surgery and Pathology.

1. Hohnfeldt, A.: Beitr. z. path. Anat. u. z. allg. Path. **3**:343, 1888.
2. Kiyono, K.: Die vitale Karminspeicherung, Jena, Gustav Fischer, 1914, p. 94.
3. Sabin, Florence R.: Bull. Johns Hopkins Hosp. **34**:277, 1923.
4. Maximow, A. A.: Arch. Path. **4**:557, 1927.
5. Rokitansky, Carl: A Manual of Pathological Anatomy, London, Sydenham Society, 1850, vol. 3, p. 23.

METHODS

Turpentine and croton oil, either pure or in various dilutions with refined cotton seed oil, when injected subcutaneously into the lumbar region, produced too diffuse a type of inflammation and were discarded as unsatisfactory. Various dilutions of aleuronat, however, were tried, and experience showed that a fresh 8 per cent solution was most successful in producing definitely localized inflammatory reactions. Intracutaneous injections induced necrosis of the superficial layers of the skin, subsequent evacuation and rapid healing. Intramuscular injections induced a too diffuse reaction, and there was much less cytologic response from muscle than from loose areolar tissue. Subcutaneous injections proved most satisfactory, and a site in the region of the loin, less disturbed by muscular activity, was selected for study. A preparation of graphite, known as "hydrokollog 300," and a 2 per cent solution of trypan blue were used as vital dyes during these observations; epinephrine hydrochloride and phenolsulphonphthalein were also used to test the absorption from the lesions.

OBSERVATIONS

Cellular reactions induced subcutaneously in the loin in rabbits by aleuronat were such as characterize any field of inflammation. During the first two days neutrophilic leukocytes predominated, and there was partial necrosis along the inner part of the pyogenic wall. After the second day, however, there was marked decrease in the number of these granulocytes with an accompanying increase in lymphocytes, monocytes and macrophages. Ordinarily about the seventh day, but occasionally before, large numbers of eosinophilic leukocytes were present. Likewise, during the latter periods, fibroblasts were abundant.

When a preparation of graphite or a solution of trypan blue was injected into the posterior region of the loin in normal rabbits, the material was readily absorbed and was very easily traced through lymph vessels to regional lymph nodes. The iliac nodes were ordinarily first discolored, but the inguinal nodes were also occasionally involved. From the iliac lymph nodes vessels were easily traced to the lower lumbar nodes and thence to the cisterna chyli and the thoracic duct. If, however, either graphite or trypan blue was injected into an abscess a day old, pigment was never identified in any of the regional lymph nodes until two weeks had elapsed.

A series of abscesses was studied at successive intervals after the injection of graphite into them, in order to determine the dispersion through the lesion and the extent of the absorption. At five and seven days after the injection of aleuronat there was no absorption, and microscopic observations showed complete thrombosis of the blood vessels and lymph vessels (fig. 1). At nine days considerable cellular activity was displayed as evidenced by the dispersion of graphite, and gradually thrombi were removed; by the sixteenth day both blood and lymph vessels were again patent (fig. 2). Occasionally macrophages containing pigment were found in small vessels, but it was clear that most of the injected pigment was removed by way of the lymph stream.

Fig. 1.—Abscess of seven days' duration. There is graphite against the inner wall, with no dispersion; the vessels are thrombosed; × 65.

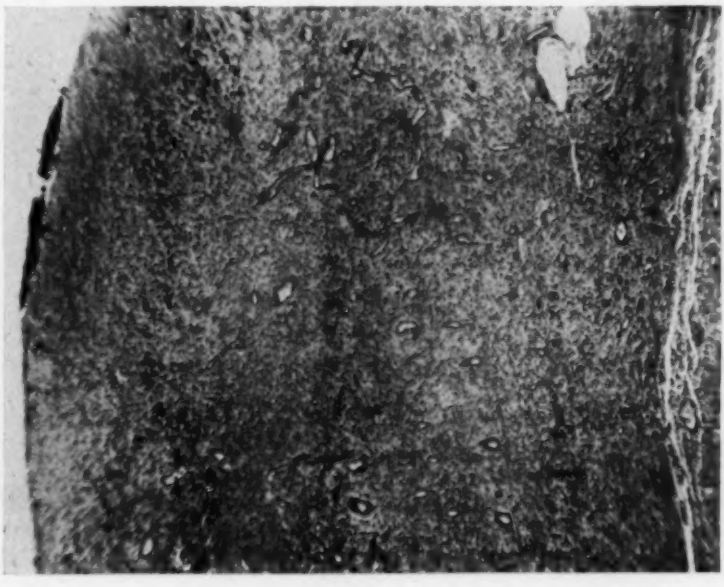

Fig. 2.—Abscess of sixteen days' duration. Graphite is scattered through the wall, and the vessels are patent; × 32.

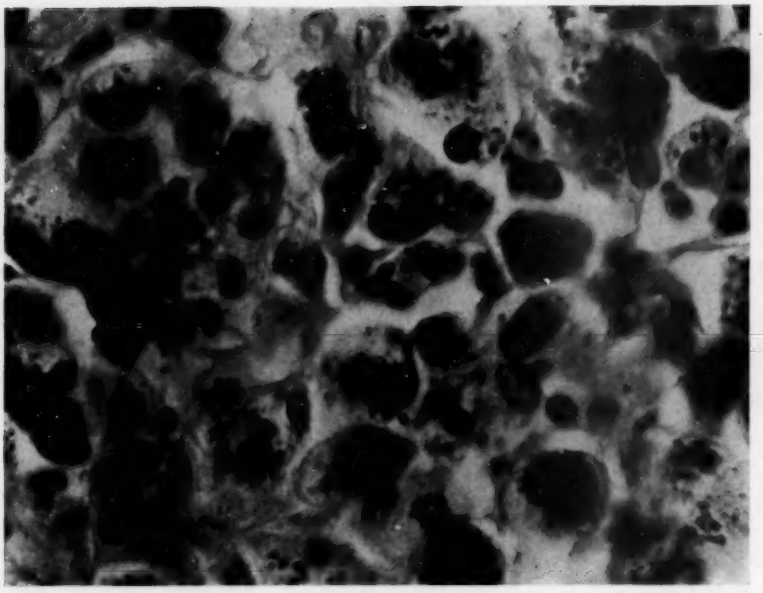

Fig. 3.—Macrophages with trypan blue in an abscess 28 days old. The granules are in rosette formation; × 700.

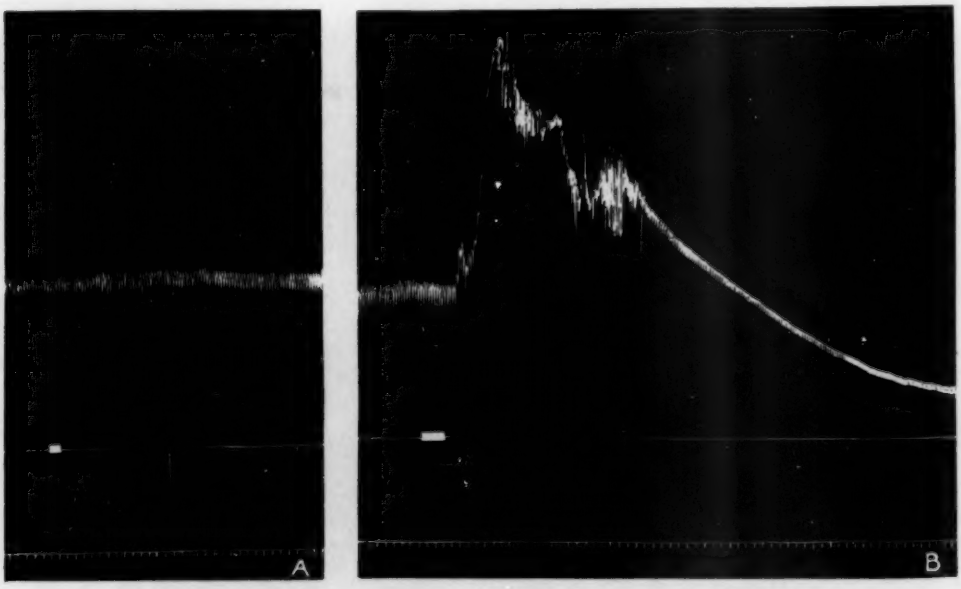

Fig. 4.—The response in blood pressure to an injection of epinephrine hydrochloride. *A* represents the response in a rabbit in which 1 cc. of a 1:1,000 dilution of epinephrine was injected into a normal subcutaneous area; *B*, that of a rabbit in which the same dose was injected into the outer wall of an abscess. Epinephrine hydrochloride was absorbed quickly when injected into the hyperemic wall of the abscess, which was 28 days old.

A comparable result was attained in a series of abscesses, from 1 to 34 days old, into which 2 cc. of a 2 per cent solution of trypan blue was injected a few days before necropsy (fig. 3). It was clear from both gross and microscopic studies that absorption, as revealed by the presence of the dye in lymph vessels and lymph nodes, did not occur until the fourteenth day. Thereafter, and until the concluding observations were made on an abscess 35 days old, pigment-laden macrophages identical with those seen in the abscess itself were recovered from the related lymph nodes.

Besides the vital dyes, various drugs were used to test absorption from these experimental abscesses. Luckhardt and Koppányi [6] showed

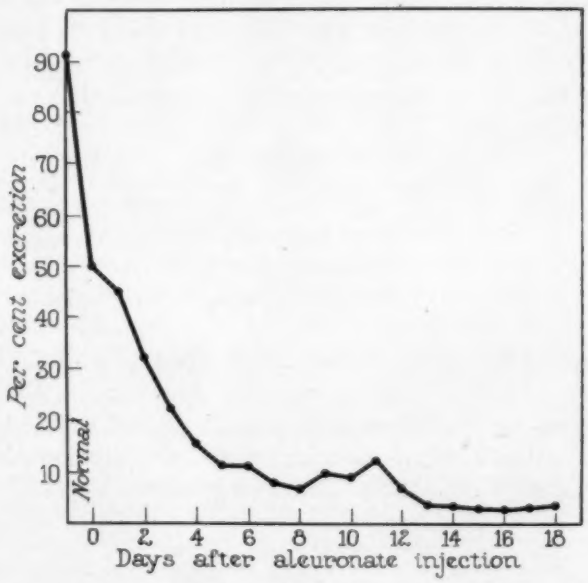

Fig. 5.—The average daily absorption and excretion of phenolsulphonphthalein from abscesses of six rabbits.

that a rise in blood pressure followed the subcutaneous injection of epinephrine hydrochloride into dogs only when the region was massaged. Accordingly, with animals anesthetized with sodium iso-amyl-ethyl barbiturate (sodium amytal) determinations of blood pressure were made directly from the carotid artery in animals that had received small dilutions of epinephrine into subcutaneous spaces as well as into abscessed areas. It was clear that absorption of the drug from abscesses a few days old could not be detected by any changes in blood pressure. On the other hand, a marked rise in blood pressure was obtained follow-

6. Luckhardt, A. B., and Koppányi, Theodore: Am. J. Physiol. **81**:436, 1927.

ing the injection of a comparable solution of epinephrine into the cavity of an abscess 4 weeks old (fig. 4).

Colorimetric tests of samples of urine, as a means of determining the extent of absorption of phenolsulphonphthalein from subcutaneous areas of normal rabbits and from abscesses in varying stages of development, gave essentially the same results. When the dye was injected daily into experimental abscesses from the time of their inception up to thirty days, and two hour samples of urine compared with a standard solution, I observed a persistent decrease in the amount of absorption until about the sixth or eighth day. Forty-five per cent of the dye introduced into an abscess 1 day old was recovered from the urine; but this percentage dropped progressively until the sixth or eighth day and remained as low as from 3 to 5 per cent until about the twentieth day (fig. 5). In normal rabbits, serving as controls, daily absorption and excretion of the dye from these same regions occurred at rates varying from 70 to 90 per cent.

COMMENT

These observations fully substantiate the conclusions hitherto stated in the literature, that absorption from subcutaneous regions takes place either through the lymph channels or through the blood capillaries, and that the route taken by an absorbed material is to a large extent determined by the physical characteristics of the substances absorbed. In other words, the absorption of particulate, granular material or of colloidal suspensions is to a large extent a function of the lymphatic system, whereas true solutions, or even finely divided colloidal solutions, are absorbed into the blood vascular system, and eliminated from the body by the components of the excretory system.

SUMMARY

The difference in absorption from an abscess as compared with a normal subcutaneous area is one of degree rather than of mechanism. The blockage established for particulate materials is regional and complete between the first and ninth days. The blockage for soluble materials is limited to the inner wall of the abscess and is not established until after from four to six days, after which the excretion remains low. An experimental abscess is most efficiently walled off between the sixth and twelfth days.

PHARYNGO-ESOPHAGEAL DIVERTICULUM

WITH SUBDIVERTICULAR ESOPHAGEAL STENOSIS, FOREIGN BODY IMPACTION AND SUDDEN DEATH: REPORT OF A CASE

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Much has been written in recent years about esophageal diverticulum, especially about the "boundary diverticulum," or pharyngo-esophageal diverticulum. The following report of a case is submitted because of its bearing on the etiology and termination of this condition.

REPORT OF CASE

A well developed white man, aged 61, came to coroner's autopsy. He was unmarried and lived alone. It was believed by the coroner that he had not eaten previously for three days because of lack of funds. He entered a cheap restaurant, and while eating a twenty-five cent dinner suddenly arose and without a sound walked toward the door, where he fell to the floor and was dead when help arrived. None of those present noticed him choking or any peculiarity in his manner of eating. His relatives stated that he had been in excellent health.

Autopsy.—The coelomic organs were examined first. There was no change in the heart or great vessels with the exception of acute dilatation of the right chambers of the heart. The lungs were large and rather boggy posteriorly, but free from consolidations. When they were sectioned, the surfaces were deep red and moist, and abundant dark red fluid dripped away. The stomach was moderately distended with poorly masticated food. There were a few capillary hemorrhages dotting the mucosa, but nothing else of importance was seen.

When the organs of the neck were removed en masse, there was seen a bulging of the posterior wall of the pharynx, with its lowest portion 1 cm. below the lower border of the cricoid cartilage, or 8 cm. below the tip of the epiglottis. The structure stood 1.5 cm. above the level of the adjacent esophagus and measured 4.5 cm. in length and 3.4 cm. in breadth (figure). As the fascia was carefully dissected away, the longitudinal muscle layer of the esophagus was found to fan out over the lower border of the sac, leaving a few scattered muscle fibers over the main mass, while on each side laterally was a heavy bundle of skeletal muscle forming an erect "Y." The upper border of the sac was on the same level as the superior border of the cricoid. Here the horizontal muscle fibers of the inferior pharyngeal constrictor crossed over the superior border of the sac. The long axis of the sac was directed posteriorly and inferiorly, with only the lower 1 cm. overhanging the posterior esophageal wall. When the sac was laid open (figure), it was found packed with shreds of poorly masticated meat. At the inferior border of the sac was a constriction of the mouth of the esophagus with a diameter of 0.4 cm. and a circumference of 1.3 cm. The opening from the pharynx into the diverticulum

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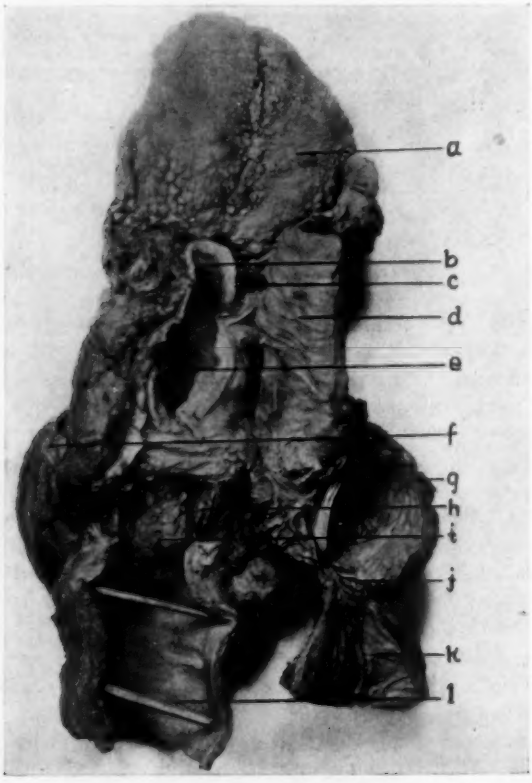
measured 4 cm. in circumference. Grossly there appeared to be only slight fibrous thickening in the submucosa, with a moderately increased circular layer of muscle outside this in the esophageal wall. The stricture was 0.9 cm. in length; the esophagus rapidly widened below to a circumference of 4.5 cm. within a distance of 2 cm. below the stricture. The wall of the sac varied from 1 to 2 mm. in thickness. The lining epithelium was gray and slightly roughened. The remainder of the wall was composed of slightly thickened fibrous tissue with little, if any, muscle. The posterior pharynx and pyriform recesses were likewise filled with



Photograph of the organs of the neck illustrating the essential points of interest of the esophageal diverticulum: (*a*) tongue, (*b*) epiglottis, (*c*) epiglottic vallecula, (*d*) pharyngeal wall (dissected laterally), (*e*) laryngeal aditus, (*f*) left thyroid lobe, (*g*) anterior view of diverticulum (dissected laterally), (*h*) cricoid cartilage, (*i*) mass of meat in larynx, (*j*) subdiverticular stricture, (*k*) esophagus and (*l*) trachea.

poorly masticated meat extending through the glottis and into the larynx. Wedged between the vocal cords, entirely filling the larynx, was a single tough mass of incompletely chewed meat and fascia measuring 4 by 3 by 1.5 cm. Beneath this in the trachea and main bronchi were other smaller pieces and shreds of tough meat, together with an abundance of mucus. The lining mucosae of the trachea, larynx and pharynx were pale, pinkish gray and smooth, and showed no swelling.

Microscopic sections cut longitudinally through the narrowed point revealed the intact covering of stratified squamous epithelium with no horny layer. There was no thickening of the lamina propria; a moderate increase in the normal content of lymphocytes and scattered plasma cells were observed here. The muscularis mucosae was composed of intermittent rather heavy bands of smooth muscle disposed longitudinally, and was absent in intervening areas. The submucosa was composed of loose fibrous tissue, free from cellular infiltration and not appreciably thickened. There were no glands present. The lamina muscularis measured 1.5 to 2.5 mm. in thickness. The inner circular layer blended imperceptibly with the outer thin longitudinal fibers through intervening oblique strands. The tunica externa was made up of loose fibro-areolar connective tissue mixed with fat. There was no cellular infiltration here.

Horizontal sections taken from the lower end of the wall of the diverticulum revealed the mucosa to be slightly redundant and folded on itself. The loose fibro-areolar tissue of the mucosa and submucosa merged without demarcation owing to the absence of muscularis mucosae or elastic membrane. An abundant lymphocytic infiltration was found below the epithelium at one point. Deep beneath this was a solitary lymph follicle with hyperplastic germinal center. A single clump of mucous glands infiltrated heavily by small lymphocytes was seen. Leading away from this was a large duct lined by a double to triple layer of cuboidal epithelium containing in the lumen a small quantity of amorphous, pale-staining material with a small quantity of yellow granular pigment. Closely surrounding the duct were numerous plasma cells. There was a thin, incomplete layer of irregularly disposed voluntary muscle with predominant circular arrangement. In some places, this failed completely and was supplanted by loose fibrous tissue, with an occasional muscle fiber or bundle circularly placed. Only a few isolated longitudinal muscle fibers were present.

Sections cut horizontally from the midportion of the diverticulum showed a transition from normal, noncornifying, stratified squamous epithelium on one end, through a patch of partially necrotic epithelium with heavy neutrophilic infiltration to a large area of complete epithelial necrosis covered with polymorphonuclear leukocytes entangled in fibrin. Numerous neutrophils and eosinophils were found here and in the connective tissue just beneath. In the underlying loose connective tissue, the capillaries were dilated, and the tissue meshes were filled with plasma cells, round cells and neutrophils in about equal numbers. Several hyperplastic solitary lymph follicles lay in this region. Again, outside this, was a rather thick layer of loose fibrous connective tissue containing numerous arterioles, the walls of which were thickened by almost acellular hyaline connective tissue. Only scattered plasma cells and histiocytes were encountered here. There was a single group of skeletal muscle fibers, which were placed in longitudinal manner.

COMMENT

The etiology of pharyngo-esophageal diverticulum has long been disputed, some authors [1] holding that the outpocketing is congenital or due to congenital defect, while others [2] have maintained that it is due to

1. Mosher, H. P.: Laryngoscope **34**:854, 1924. Oehlecker, F.: Arch. f. klin. Chir. **134**:699, 1925.

2. Kraas, E.: Klin. Wchnschr. **9**:1457, 1930. Lotheissen, George: Ergebn. d. Chir. u. Orthop. **23**:110, 1930.

mechanical means, by evagination of the mucosa and submucosa through a weak point in the muscular wall in the presence of increased intra-esophageal pressure. This weak point is the triangle described by Laimer (cited by Lotheissen [2]) on the posterior pharyngeal wall at the union of the esophagus and pharynx where the longitudinal esophageal muscle fibers diverge to unite with the lower fibers of the inferior pharyngeal constrictor.

Boundary diverticulum has been reported in conjunction with esophageal stenosis of various kinds. Several cases associated with compression of the esophagus by retrosternal goiter [3] have been recorded. Others [4] have described instances of pharyngo-esophageal diverticula associated with cardiospasm, and in addition Zohlen cited a personal communication from Vinson of a fourth similar case. Mosher [1] described one case of congenital malformation of the pharynx associated with diverticulum, and ascribed others to developmental errors of this kind because of the frequency of malformations of the pharynx in the cadaver. Chevalier Jackson,[5] from his vast experience with internal examination of the esophagus during life, considered the failure of the cricopharyngeus muscle to relax its normal tone during deglutition as the most important exciting factor in the formation of boundary diverticula. Sturgeon [6] concurred in this view. Keiper [7] described the anatomic changes in a case of cicatricial stenosis of the esophagus associated with cervical pulsion diverticulum, and ascribed the sacculation to this origin in most instances. However, no other similar case proved by autopsy has been found in a search of the literature, although the clinical findings in several instances [8] have suggested this etiology.

All these citations suggest that increased intra-esophageal or intra-pharyngeal pressure in conjunction with obstruction of the upper alimentary canal from the various causes may be important in the formation of this type of diverticulum. However, it is well known that marked and prolonged obstruction of the esophagus may exist with no sign of diverticularization. Vinson [9] listed 186 cases of benign cicatricial stenosis of the esophagus seen at the Mayo Clinic, but made

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3. Bouvier, E.: Arch. f. klin. Chir. **134**:802, 1925. Lerche, W.: S. Clin. North America **3**:1227, 1923. Haberer: Arch. f. klin. Chir. **122**:789, 1923; abstr., J. A. M. A. **80**:1109, 1923.

4. Fitzgibbon, J. H.: J. A. M. A. **86**:1614, 1926. Zohlen, J. P.: Wisconsin M. J. **28**:526, 1929. Abell, I.: S. Clin. North America **10**:901, 1930.

5. Jackson, Chevalier, and Shallow, T. A.: Ann. Surg. **83**:1, 1926.

6. Sturgeon, C. T.: J. A. M. A. **92**:379, 1929.

7. Keiper, G. F.: Laryngoscope **22**:1127, 1912.

8. Gaub, O. C., and Jackson, Chevalier: Surg., Gynec. & Obst. **21**:52, 1915. Küster: Arch. f. klin. Chir. **83**:613, 1907. Sturgeon (footnote 6).

9. Vinson, P. P.: Ann. Otol., Rhin. & Laryng. **36**:40, 1927.

no mention of associated diverticula in any. Downie [10] also failed to note this complication in a similar discussion of 100 consecutive obstructions of the gullet.

It then seems evident that some factor other than obstruction, possibly weakening of the wall or congenital malformation, is necessary in diverticularization. The case now reported is an example of obstruction of the esophagus and early diverticulum occurring together. In deciding the etiology of the stenosis in this case, the absence microscopically of scar tissue or cellular infiltration in the narrowed area is against postinflammatory stricture. There is no evidence of malignant growth. The relatives, when closely questioned, stated that the dead man had never complained of difficulty in swallowing but that three years before death he was observed to wash down each bolus with liquid; they told of a choking spasm that he had suffered while eating six months prior to death. Since no abnormality had been noticed before this, a congenital stenosis is unlikely. It may be fairly assumed, then, that one is dealing with a spastic closure due to increased muscle tonus. Even here one is on uncertain ground, as Mosher [1] stated that in an unfixed specimen from a cadaver, stenosis of the esophageal orifice is produced by backward pressure on the posterior pharyngeal wall. The sudden death without evidence externally of choking resulting from complete closure of the glottis in the absence of demonstrable heart disease is of medicolegal interest. The apparent rapidity with which pulmonary congestion occurred is striking. The recent acute inflammatory process in the wall of the diverticulum was probably due to decompostion of residual food or secretion in the sac.

SUMMARY

An instance of pharyngo-esophageal diverticulum with subdiverticular esophageal stenosis, foreign body impaction and sudden death is recorded, apparently due to muscle spasm in the esophagus with resulting increased pulsion in the posterior pharynx during deglutition.

10. Downie, W.: Glasgow M. J. **87**:336, 1912.

EXPERIMENTAL THROMBO-ANGIITIS OBLITERANS

BACTERIOLOGIC AND PATHOLOGIC STUDIES

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AND

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In a consideration of the causes of thrombo-angiitis obliterans, infection seems the most logical cause, in which event the infection will be of a distinctly low grade, as is shown by the usual picture of pathologic change.[1] In a study of the arteries and veins in this disease, one is impressed with the inflammatory nature of the lesions. Buerger [2] stated his belief that the disease is due to a specific infectious or toxic agent. He has succeeded in reproducing the lesion in human beings by inoculating material from acutely inflamed superficial veins of patients with thrombo-angiitis obliterans adjacent to superficial normal veins of patients who previously had had thrombo-angiitis obliterans; the lesions were not produced when he injected the material into a tied loop of a superficial vein. However, a specific agent or organism was not isolated from these lesions. He obtained negative results in animals. Rabinowitz [3] claimed to have found a gram-negative bacillus in the blood of patients with thrombo-angiitis obliterans and to have produced vascular lesions in rabbits. Jablons [4] was unable to confirm this work. The work which we report was started in November, 1927, and was continued for a period of two and a half years. It seems desirable at this time to report the relatively large number of data which has accumulated during this period.

MATERIAL AND METHODS

The material used in this investigation was obtained from fifty-six patients with thrombo-angiitis obliterans and ten patients with arteriosclerotic disease of the lower extremities. The youngest patient with thrombo-angiitis obliterans was aged 23 years, and the oldest, 73 years. One patient was a woman, aged 60 years; the

Submitted for publication, Feb. 2, 1932.

From the Division of Medicine of the Mayo Clinic.

1. Brown, G. E.; Allen, E. V., and Mahorner, H. R.: Thrombo-Angiitis Obliterans, Philadelphia, W. B. Saunders Company, 1928.

2. Buerger, Leo: Surg., Gynec. & Obst. **19**:582, 1914; Arch. Path. **7**:381, 1929.

3. Rabinowitz, H. M.: Surg., Gynec. & Obst. **37**:353, 1923.

4. Jablons, Benjamin: Internat. Clin. **3**:193, 1925.

others were men. Seventeen of the patients with thrombo-angiitis obliterans had had a leg amputated, and one patient had had a finger amputated. Gangrene was present in each extremity that was amputated. Nineteen acutely inflamed superficial veins were obtained at biopsy from the extremities of a corresponding number of patients who had thrombo-angiitis obliterans. All of the patients with arteriosclerotic disease had had an extremity amputated. In both groups, large segments of arteries and veins were dissected from the amputated extremity at the time of operation, placed in a sterile test tube and immediately taken to the laboratory, where cultures were made. A large number of sections was preserved for microscopic study. After the tissues had been washed several times with a solution of sterile physiologic solution of sodium chloride, numerous segments were embedded in tubes of soft dextrose brain agar, which had been previously melted and cooled to 40 C. Other portions were emulsified in a mortar under aseptic precautions and inoculated into tall tubes of dextrose brain broth and dextrose brain agar, the mediums of choice used by Rosenow [5] in studies of elective localization. These were then sealed with sterile petrolatum, to insure anaerobic conditions, and incubated at 37.5 C. for from twenty-four hours to five months. Subcultures were not made until the cultures showed evidence of growth. For a control series cultures were made of normal arteries and veins obtained from twenty-four other patients at surgical operations. These tissues were cultured in the same manner as those obtained from patients having thrombo-angiitis obliterans and arteriosclerosis.

RESULTS OF CULTURE

Cultures obtained from segments of veins and arteries from seventeen amputated extremities of patients who had thrombo-angiitis obliterans gave the following results: Gram-positive, pleomorphic streptococci were obtained in four instances (fig. 1 *A*), green-producing streptococci in two instances, staphylococci in three, and gram-positive bacilli in four.

Cultures were made from segments of nineteen acutely inflamed superficial veins obtained at biopsy from a corresponding number of patients with thrombo-angiitis obliterans; from three to seven cultures were made from each specimen (table 1). Gram-positive, pleomorphic streptococci were isolated from six specimens, staphylococci from seven specimens, and gram-positive bacilli from three specimens.

The cultures from an acutely inflamed vein obtained at biopsy from a man, aged 52 years (case 3, table 1), showed gram-positive, pleomorphic streptococci on the eighth day of incubation. This patient returned to the clinic three months later, and the left leg was amputated below the knee. Organisms isolated from the deep arteries and veins of the amputated extremity on the eighteenth day after incubation were morphologically the same as those previously obtained from the specimen used for biopsy.

Approximately from five to thirty-five hours after the acutely inflamed veins were first observed, they were removed surgically under

5. Rosenow, E. C.: Personal communication.

aseptic conditions. In each instance, the superficial vein and surrounding skin showed definite evidence of an inflammatory process. The skin was red, swollen and tender to palpation, and a small segment of the vessel was obviously thrombosed, as the vessel both proximal and distal to the inflamed area could be collapsed with gentle pressure, whereas the area of thrombosis appeared as a solid cord. Occasionally, the area of thrombosis could be extruded from the cut end of the vein by gentle pressure at the time of the taking of the specimen for biopsy, but in most instances the lesion was firmly adherent to the wall of the vessel.

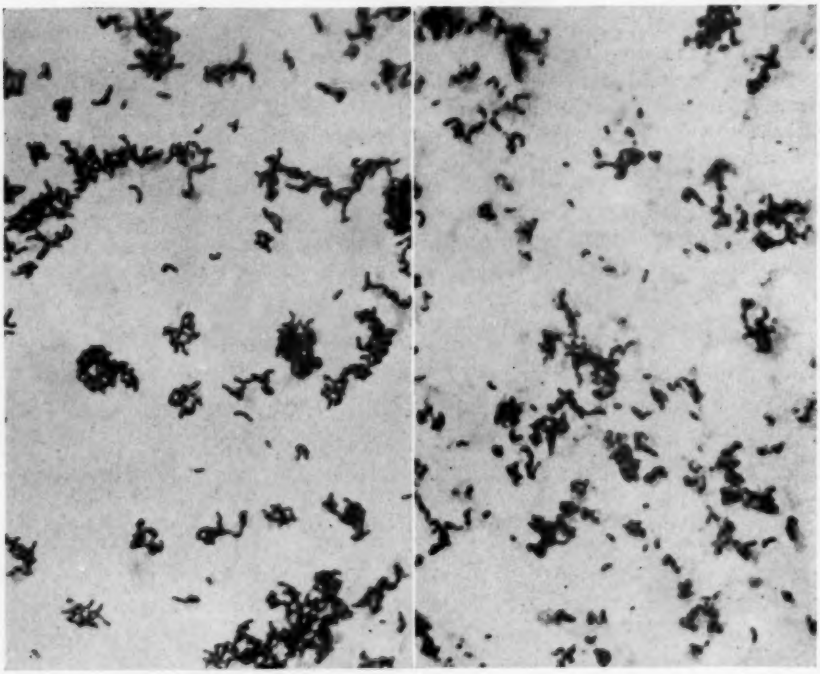

Fig. 1.—*A*, pleomorphic streptococci isolated from arteries and veins obtained at the site of amputation of a leg of a man, aged 52 years, who had thrombo-angiitis obliterans (case 3, table 1); × 1,000. *B*, pleomorphic streptococci isolated from arteries and veins obtained from an amputated leg of a man, aged 69 years (case 3, table 2), who had arteriosclerotic disease of the lower extremities; × 1,000. Gangrene was not present in the leg.

The seventh day was the minimal time and the twenty-sixth day was the maximal time at which the pleomorphic streptococcus was isolated from patients with thrombo-angiitis obliterans. The green-producing streptococcus was isolated from the vessels of the amputated leg at the end of twenty-four hours and from the vessels of the amputated finger on the eleventh day. When first isolated, the pleomorphic streptococcus appeared as a slender, gram-positive, nonmotile

bacillus, occurring singly or in pairs, closely resembling diphtheroid bacilli. In subcultures in dextrose brain broth or dextrose brain agar, its morphologic character changed so that it appeared in short, gram-positive, coccoid chains. The average chain contained from three to five organisms. These organisms were always isolated under anaerobic conditions. In subcultures they grew only under anaerobic conditions, except in three instances in which after repeated cultures they grew

TABLE 1.—*Cultures Obtained from Arteries and Veins of Patients with Thrombo-Angiitis Obliterans*

Patient	Age	Sex	Source of Tissue Cultured: Biopsy	Source of Tissue Cultured: Amputation	Period of Incubation, Days	Results
1	35	M	Vein	.....	10	Gram-positive pleomorphic streptococcus
2	23	M	Vein	.....	9	Gram-positive pleomorphic streptococcus
3	52	M	Vein	.....	8	Gram-positive pleomorphic streptococcus
				Gangrenous leg	18	Gram-positive pleomorphic streptococcus
4	25	M	Vein	.....	26	Gram-positive pleomorphic streptococcus
5	36	M	Vein	.....	16	Gram-positive pleomorphic streptococcus
6	31	M	.....	Gangrenous leg	11	Gram-positive pleomorphic streptococcus
7	33	M	.....	Gangrenous leg	9	Gram-positive pleomorphic streptococcus
8	36	M	.....	Gangrenous leg	17	Gram-positive pleomorphic streptococcus
9	59	M	Vein	.....	7	Gram-positive pleomorphic streptococcus
10	73	M	.....	Gangrenous leg	1	Green-producing streptococcus
11	25	M	.....	Gangrenous finger	11	Green-producing streptococcus
12	37	M	.....	Gangrenous leg	141	Four negative cultures
13	45	M	Vein	.....	132	Staphylococci in 1 of 5 cultures
				Gangrenous leg	82	Gram-positive cocci in 1 of 4 cultures
14	40	M	.....	Gangrenous leg	72	Five negative cultures
				Reamputation	57	Staphylococci in 1 of 5 cultures
15	42	M	.....	Gangrenous leg	68	Gram-positive bacilli in 1 of 5 cultures
16	49	M	.....	Gangrenous leg	68	Five negative cultures
17	36	M	.....	Gangrenous leg	53	Staphylococci and gram-positive bacilli in 1 of 6 cultures
18	34	M	Vein	.....	90	Six negative cultures
19	35	M	.....	Gangrenous leg	65	Six negative cultures
20	49	M	Vein	.....	120	Staphylococci in 1 of 3 cultures
21	55	M	.....	Gangrenous leg	57	Gram-positive bacilli in 1 of 5 cultures
22	57	M	Vein	.....	67	Four negative cultures
23	29	M	Vein	.....	43	Staphylococci in 3 of 5 cultures
24	60	F	Vein	.....	45	Gram-positive bacilli in 1 of 5 cultures
				Gangrenous leg	78	Ten negative cultures
25	38	M	.....	Gangrenous leg	104	Six negative cultures
26	33	M	Vein	.....	69	Eight negative cultures
27	52	M	.....	Gangrenous leg	55	Gram-positive bacilli in 3 of 6 cultures
28	49	M	Vein	.....	102	Staphylococci in 3 of 7 cultures
29	48	M	Vein	.....	86	Five negative cultures
30	31	M	Vein	.....	81	Staphylococci in 2 of 6 cultures
31	43	M	Vein	.....	65	Staphylococci in 1 of 3 cultures
32	34	M	Vein	.....	87	Four negative cultures
33	30	M	Vein	.....	79	Staphylococci in 2 of 4 cultures
34	40	M	.....	Gangrenous leg	104	Eight negative cultures

slowly on the surface of horse blood agar plates. Except in these three instances, neither the primary cultures nor the subcultures were grown on blood agar plates under aerobic conditions. The colonies on blood agar plates appeared as colorless, pinpoint-sized, dry, translucent bodies, showing neither hemolysis nor formation of pigment. Subcultures in dextrose brain broth or dextrose brain agar also grew very slowly, the growth first appearing at from the third to the sixth day. The pleomorphic streptococcus was never found associated with other micro-organisms. The negative cultures were allowed to incubate for from sixty-five to one hundred and forty-one days at 37.5 C. The

green-producing streptococci grew readily in primary culture on blood agar plates and in dextrose brain broth. They also grew from the embedded vessels and emulsion in from twenty-four to forty-eight hours.

A similar study was made of arteries and veins from amputated extremities obtained from ten patients with arteriosclerotic disease of the lower extremities. The youngest patient was aged 49 years, and the oldest, 78 years. The vessels were obtained under aseptic conditions at the site of the amputation and were cultured in a manner similar to that previously described for the patients with thrombo-angiitis obliterans. Gram-positive, pleomorphic streptococci were isolated from the arteries and veins of five patients (fig. 1 *B*). Cultures from the arteries and veins of four did not contain organisms; one of ten cultures

TABLE 2.—*Cultures Obtained from Arteries and Veins of Ten Patients with Arteriosclerosis* *

Age	Sex	Cultures Incubated, Days	Results
68	M	24	Pleomorphic streptococcus
71	M	2	Pleomorphic streptococcus
69	M	21	Pleomorphic streptococcus
70	M	9	Pleomorphic streptococcus
71	M	9	Pleomorphic streptococcus
78	M	150	Four negative cultures
55	M	152	Two negative cultures
66	M	72	Five negative cultures
49	M	20	Gram-positive bacillus in 1 of 10 cultures
68	F	38	Six negative cultures

* The arteries and veins were obtained at the time, and at the site, of amputation of the leg. Gangrene was present in one or more toes of all the extremities amputated with the exception of the third case.

showed gram-positive bacilli on the twentieth day of incubation. All of these cultures were incubated at 37.5 C. for from four to one hundred and fifty-two days. The earliest time at which the pleomorphic streptococci appeared was on the fourth day, and the latest time, the twenty-fourth day. A summary of the cultures of arteries and veins obtained from patients having arteriosclerosis is shown in table 2.

For a control study, cultures were made of normal arteries and veins obtained from twenty-four other patients in the course of various types of operations (table 3). Sixteen of the cultures did not yield growth; seven contained gram-positive cocci, and one, a gram-positive bacillus.

The pleomorphic streptococci obtained from nine patients with thrombo-angiitis obliterans were grown in 150 cc. of dextrose brain broth for from six to eighteen days at 37 C. From 0.1 to 0.5 cc. was inoculated into eleven different sugars, with results as follows: All fermented dextrose; four lactose; five, saccharose, salicin and maltose; two, mannite; six, raffinose; nine, galactose; eight, levulose, and eight,

inulin and rhamnose. Two produced acid in litmus milk, and two, acid and coagulation. The micro-organisms from all the patients grew readily on Drigalski-Conradi agar and litmus lactose agar. The colonies appeared very small and colorless and were embedded in the agar.

The pleomorphic streptococci obtained from arteries and veins of five patients with arteriosclerosis were inoculated into the same eleven sugars with results as follows: Five fermented dextrose; one, lactose; one, saccharose; none, salicin; one, maltose, mannite and raffinose; two, galactose; five, levulose; one, inulin, and one, rhamnose. One produced acid in litmus milk, and one, acid and coagulation. Growth appeared in

TABLE 3.—*Cultures Obtained from Arteries and Veins of Twenty-Four Normal Subjects*

Source of Tissue Cultured	Period of Incubation, Days	Results
Abdominal wall	160	Three negative cultures
Abdominal wall	160	Three negative cultures
Great omentum	160	Three negative cultures
Muscle from neck	154	Three negative cultures
Abdominal wall	154	Three negative cultures
Muscle from neck	9	Staphylococci in 1 of 3 cultures
Great omentum	154	Three negative cultures
Great omentum	154	Three negative cultures
Subcutaneous tissue from leg	8	Staphylococci in 1 of 3 cultures
Subcutaneous tissue from leg	5	Staphylococci in 1 of 3 cultures
Subcutaneous tissue from knee	134	Three negative cultures
Subcutaneous tissue from hip	122	Three negative cultures
Subcutaneous tissue from knee	91	Three negative cultures
Muscle from leg	1	Three cultures contained staphylococci
Muscle from hip	7	Gram-positive bacilli in 1 of 4 cultures
Muscle from leg	9	Staphylococci in 2 of 6 cultures
Muscle from leg	23	One negative culture
Muscle from leg	43	Two negative cultures
Abdominal wall	5	Staphylococci in 1 culture
Great omentum	60	One negative culture
Great omentum	60	One negative culture
Great omentum	5	Staphylococci in 1 culture
Great omentum	60	Two negative cultures
Great omentum	60	One negative culture

Drigalski-Conradi agar and litmus milk in all except one case. Growth was not observed on either potato or endo-agar plates.

Comment.—The pleomorphic streptococci that were obtained from the arteries and veins of patients with thrombo-angiitis obliterans and arteriosclerosis seemed to be morphologically identical, and the cultural characteristics were for the most part similar. It is the general belief that low grade infection is the etiologic basis for thrombo-angiitis obliterans, as is observed in the usual pathologic picture. On the other hand, most observers do not regard arteriosclerosis as of infectious origin. It is possible that in the cases included in this report under the heading "arteriosclerosis," a so-called mixed type of lesion may have been present, as was demonstrated in one of the five positive cultures of pleomorphic streptococci. The patient was a man, aged 71 years (case 2, table 2). Clinically and from microscopic study of the vessels, these cases must be classified as representing senile arteriosclerosis, but it is

possible that some of the patients may have had thrombo-angiitis obliterans in a mild form at an earlier date. This is borne out by a recent report on a study of thrombo-angiitis obliterans of aged patients.[6] One of the patients in this group, a man aged 73 years, had thrombo-angiitis obliterans, as was proved by study of the vessels of the amputated extremity and later at necropsy (case 10, table 1). Ordinarily from a clinical standpoint and from microscopic study of an occasional vessel, this patient would have been reported as having arteriosclerosis, primarily because of his age, but age itself does not exclude the presence of thrombo-angiitis obliterans. It is also true that large segments of vessels were used for culture, and no attempt was made to obtain serial sections of segments of similar size for microscopic study. This may be of definite significance, since the lesions of human beings with thrombo-angiitis obliterans are distinctly patchy in distribution. A small segment of a vessel may often be seen to be occluded, yet the vessel both proximal and distal to the lesion will appear to be normal. If any significance can be attached to the various organisms isolated in this study, it must be with reference to the pleomorphic streptococcus. The other organisms represent either contaminants or secondary invaders present because of gangrene.

RESULTS OF INJECTION IN ANIMALS

Experiments on animals seemed necessary in order to attempt to evaluate the etiologic significance of the pleomorphic streptococci that were obtained from the arteries and veins of patients with occlusive vascular diseases.

One hundred and fifteen male rabbits and three dogs were used in the experiments. Injections were made as follows: 1. Organisms were injected intravenously into thirteen rabbits. 2. Organisms were injected into the femoral muscles adjacent to the femoral vessels in forty-two rabbits. 3. Portions of blood vessels of human beings were embedded adjacent to the femoral vessels in twenty-nine rabbits and one dog. 4. Vessels that had been previously shown to contain pleomorphic streptococci were embedded in the pulp cavities of teeth of two dogs. 5. Micro-organisms obtained from foci (teeth, tonsils, nasopharynx and prostate gland) were injected intravenously into thirty-one rabbits.

Thirteen white male rabbits were given intravenous injections for three successive days with from 5 to 12 cc. of a culture of pleomorphic streptococci in dextrose brain broth (table 4). These cultures were obtained from arteries and veins of seven patients. They represented vessels obtained at biopsy from four patients with thrombo-angiitis obliterans, vessels from amputated extremities of two patients with

6. Horton, B. T., and Brown, G. E.: Ann. Int. Med. **5**:613, 1931.

thrombo-angiitis obliterans, and vessels from an amputated extremity of one patient with arteriosclerosis. Six rabbits died at the end of from four to fifty-seven days, and seven were chloroformed at the end of from three to seventy-five days. Intimal proliferation and thrombosis

TABLE 4.—*Summary of Results on Experimental Animals*

Method of Producing Lesions	Patients from Whom Material Was Obtained	Diagnosis: Thrombo-Angiitis Obliterans	Diagnosis: Arterio-sclerosis	Source of Material: Biopsy	Source of Material: Amputation	Rabbits Used	Results and Comment
Pleomorphic streptococci injected intravenously into veins of ears of rabbits	7	6	1	3	4	13	Sections of femoral vessels from 2 rabbits showed thrombosis and intimal proliferations. Pleomorphic streptococci isolated from an acutely inflamed vein of a patient with thrombo-angiitis obliterans had been injected
Pleomorphic streptococci placed adjacent to femoral vessels	15	11	4	5	10	42	Sections of femoral vessels from 10 rabbits showed thrombosis and intimal proliferation. Pleomorphic streptococci isolated from vessels of patients with thrombo-angiitis obliterans had been injected into seven rabbits, and streptococci from patients with arteriosclerosis had been injected into three
Arteries and veins placed adjacent to femoral vessels	16	16	0	9	7	29	Sections of femoral vessels from 7 rabbits showed thrombosis and intimal proliferation, and trophic changes and dry gangrene developed in toes of hind feet of one rabbit
Green-producing streptococci, indifferent streptococci, diplococci and Micrococcus catarrhalis injected intravenously	5	5	0	2 teeth 2 tonsils 1 swab from nasopharynx		9	
	2	0	2	1 tonsil 1 gangrenous toe		2	
Washings from swab of ulcer, green-producing streptococci and Micrococcus catarrhalis injected adjacent to femoral vessels	1	1	0	Ulcer of foot		1	
	1	1	0	Tonsil		1	Negative; intimal proliferation and thrombosis not produced
Tonsil placed adjacent to femoral vessels	1	1	0	Tonsil		1	
Green-producing streptococci and Micrococcus catarrhalis injected into testes	1	1	0	Nasopharynx		1	
Micro-organisms injected intravenously	13	13	0	Prostate gland		16	

took place in the deep veins of the extremities of two rabbits. These two rabbits had been given intravenous injections of streptococci that had been isolated from an acutely inflamed vein of a patient having thrombo-angiitis obliterans. Microscopic sections (stained by Gram's method modified by Rosenow) of arteries and veins from the extremities of seven rabbits did not show micro-organisms. Cultures

obtained from the blood of the heart, the kidneys and the knee joints, were negative except in two rabbits. One rabbit (given organisms isolated from an acutely inflamed vein of a subject with thrombo-angiitis obliterans) lived four days, and positive cultures of pleomorphic streptococci were obtained from the blood of the heart, the joints and the kidneys. The blood of the heart from another rabbit on the sixteenth day contained organisms morphologically similar to those that had been injected previously. The organisms were originally isolated from the vessels of an amputated extremity of a patient with thrombo-angiitis obliterans. All cultures were incubated for thirty days or longer at 37 C.

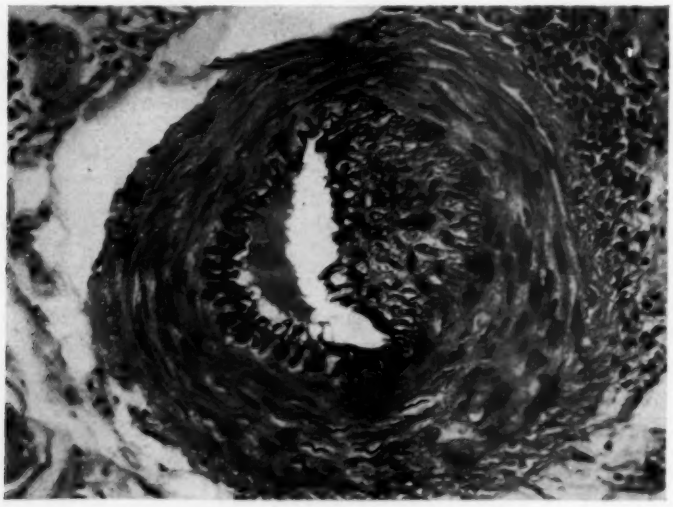

Fig. 2.—Cross-section of a small artery from the femoral group of muscles of a rabbit showing proliferation of the intima and infiltration of the adventitia by round cells; × 250. Pleomorphic streptococci obtained from arteries and veins of an amputated extremity of a man with thrombo-angiitis obliterans (case 10, table 1) had been injected at a site adjacent to the femoral vessels. Local reaction had not developed at the site of injection. The rabbit had been killed sixteen months later.

Forty-two rabbits were inoculated with pleomorphic streptococci adjacent to the femoral vessels. The streptococci were obtained from fifteen patients, eleven of whom had thrombo-angiitis obliterans and four arteriosclerosis (table 4). Twenty-three of the forty-two rabbits lived from three to one hundred and ninety-eight days, and the remaining nineteen were killed at irregular intervals of from two to four hundred and eighty-nine days. Intimal proliferation and thrombosis took place in the femoral vessels of ten rabbits. Organisms from three specimens obtained on amputation and from three obtained at biopsy

from six patients with thrombo-angiitis obliterans were injected into seven of these rabbits. Three of the rabbits were given injections of organisms obtained from amputated extremities of patients with arteriosclerosis. Essentially the same lesions were observed following the injection of organisms obtained from patients with thrombo-angiitis obliterans as following the in ection from those patients with arteriosclerosis (figs. 2, 3 and 4). Gram-positive diplococci were found in the intima, media or adventitia of the femoral vessels of eight rabbits, and in four additional rabbits intimal proliferation and thrombosis were not present. Cultures from the blood of the heart, joints, kidneys and prostate gland were all negative, except for an occasional contamination

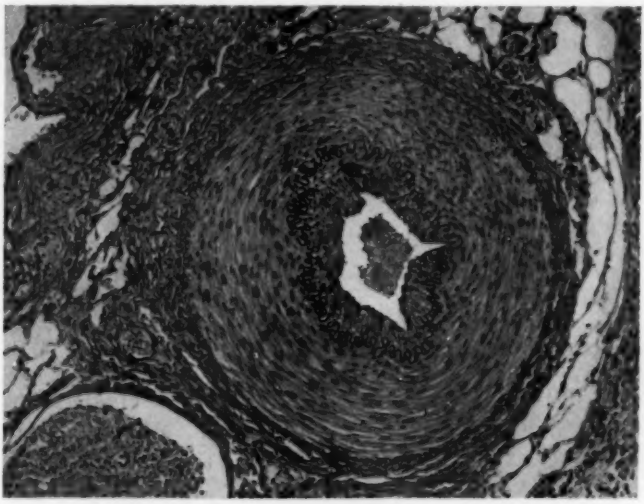

Fig. 3.—Cross-section of a femoral artery from a rabbit; × 100. It shows proliferation of the intima. Pleomorphic streptococci isolated from arteries and veins of an amputated extremity of a patient with arteriosclerosis (case 4, table 2) had been injected at a site adjacent to the vessel, and a local abscess had developed at the point of injection. The rabbit had been killed on the twentieth day.

with staphylococci or with gram-negative bacilli. The cultures were incubated from twenty-six to one hundred and eighty-six days.

Segments of arteries and veins from sixteen human beings with thrombo-angiitis obliterans were embedded adjacent to the femoral vessels in the muscles of the thighs of twenty-nine rabbits and one dog (table 4). Vessels obtained at biopsy were embedded in nine rabbits and one dog, and vessels from amputated extremities were embedded in twenty rabbits. The fourteen rabbits that died lived from four to one hundred and sixty-eight days. The fifteen rabbits that were killed lived from forty to one hundred and eighty-nine days. At necropsy,

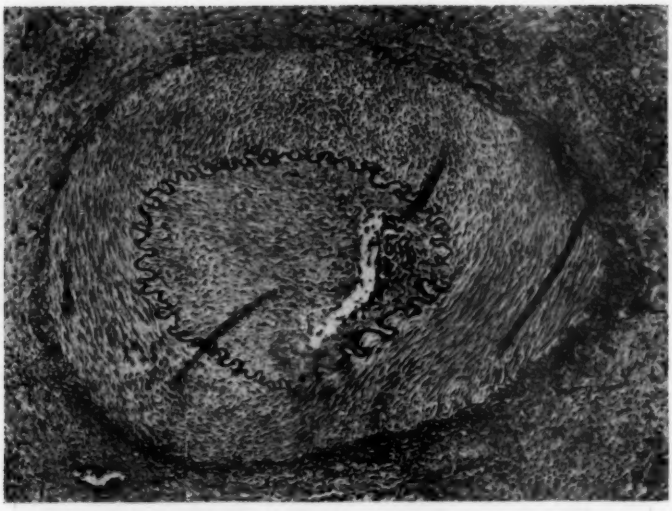

Fig. 4.—Cross-section of femoral artery from a rabbit; × 85. It shows an organized occluding thrombus surrounded by leukocytic infiltration. Pleomorphic streptococci obtained from arteries and veins of an amputated extremity of a patient with arteriosclerosis (case 4, table 2) had been injected at a site adjacent to this vessel. Local reaction had not developed. The rabbit had died fifteen days later.

Fig. 5.—Cross-section of femoral artery of a rabbit; × 85. It shows proliferation of the intima. A small segment of an artery obtained from a patient with thrombo-angiitis obliterans (case 27, table 1) had been embedded adjacent to the femoral artery. Local reaction had not developed. The rabbit had been killed at the end of one hundred and sixty-four days.

cultures obtained from the blood of the heart, joints, kidneys and prostate gland were negative after incubation for from twenty-six to seventy-five days. Micro-organisms resembling those previously described were found in the wall of, and in the tissue surrounding, the femoral veins and arteries of seven animals. The results of the experiment in the dog were negative. Intimal proliferation and thrombosis took place in the femoral vessels of seven rabbits (figs. 5 and 6), and in one rabbit trophic changes and dry gangrene were observed in the toes of the hind feet.

An acutely inflamed vein (fig. 7) obtained at biopsy from a patient with thrombo-angiitis obliterans (case 9, table 1) was embedded adjacent to the right femoral vessels in the right thigh, of a rabbit,

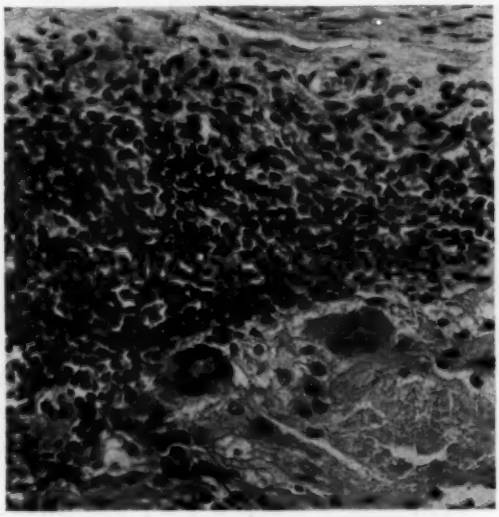

Fig. 6.—Adventitial coat of femoral artery from a rabbit, showing infiltration by round cells, with the formation of giant cells. An acutely inflamed vein obtained at biopsy from a patient with thrombo-angiitis obliterans (case 22, table 1) had been embedded in a position adjacent to the femoral artery. The rabbit had died fifty-nine days later. Local reaction had not developed at the site of the embedded tissue.

May 18, 1929. The other extremities were not disturbed. Gangrene of the toes of both hind feet had developed by June 15, 1929, and the surface temperature of the hind feet decreased markedly (fig. 8). The front feet remained normal. From a clinical standpoint, the gangrene of the toes suggested that observed in human beings with thrombo-angiitis obliterans. The rabbit was killed on June 27, 1929, and a complete postmortem examination was carried out. The femoral arteries and veins, the popliteal arteries and veins and the anterior and posterior arteries and veins were normal, but characteristic occlusive

vascular lesions, such as were observed in the femoral vessels of the other rabbits, were found in the small arterioles of the hind feet. The arteries and arterioles in the fore extremities were normal. Arteriosclerotic changes were not observed in any of the vessels. Streptococci were isolated by Rosenow from the vessels of the animal, which appeared to be identical with those isolated from and demonstrated in a section of the acutely inflamed vein of the patient.

Six rabbits were given intracerebral injections of the streptococci obtained from the vessels of the rabbit, and in one of the six thrombosis of the vessels of the brain was found. Four rabbits were given intramuscular injections in the extremities, and in one rabbit thrombosis

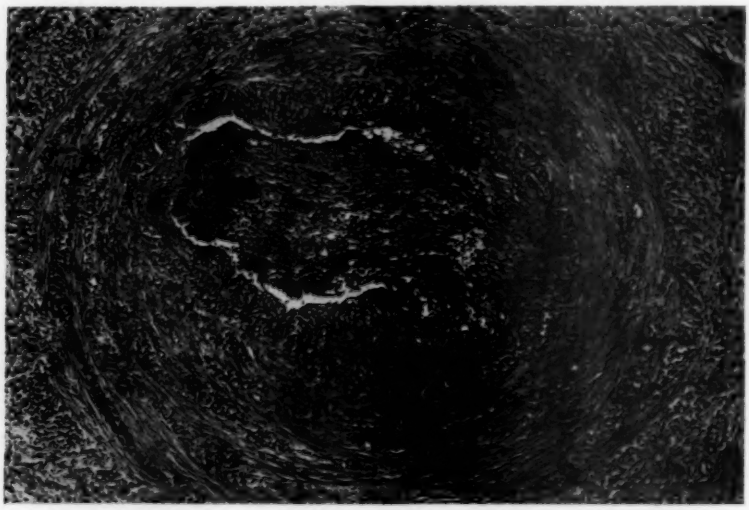

Fig. 7.—Cross-section of an acutely thrombosed vein obtained at biopsy from a patient with thrombo-angiitis obliterans (case 9, table 1). Diffuse chronic inflammatory reaction may be noted throughout the entire wall. Diplococci were found in the wall of the vein.

was found. In three rabbits that were given intravenous injections, results were negative.

Under anesthesia with iso-amyl-ethyl barbituric acid (amytal), the lower cuspid teeth of two dogs were cut off at the line of the gums, and the pulp cavities were cleaned out. A small portion of an acutely inflamed vein in which pleomorphic streptococci had been demonstrated seven days after incubation at 37 C. was obtained at biopsy from a patient with thrombo-angiitis obliterans. This was placed in the pulp cavity of one dog. Five tenths of a cubic centimeter of sediment from 150 cc. of dextrose brain broth containing green-producing streptococci that had been previously isolated from a vein of an amputated leg of a

patient with thrombo-angiitis obliterans (case 10, table 1) was injected into the pulp cavity of the second dog, and the cavities were closed with amalgam fillings. These dogs were observed over a period of two years. Clinical evidence of occlusive vascular disease in the extremities did not develop. The arterial pulsations in the extremities remained normal during this period, and the appearance of the devitalized teeth was not changed. The dogs were not killed for further study.

Since it seems to be well established that foci of infection play a part in the production of many diseases, it was thought advisable to make cultures from various foci of infection in patients with occlusive vascular diseases, and to inject the cultures into rabbits (table 4). Green-producing streptococci were the organisms predominating. Cultures containing green-producing streptococci obtained from apexes of teeth of two patients with thrombo-angiitis obliterans were injected intravenously into six rabbits; streptococci were obtained in culture

Fig. 8.—Trophic changes and dry gangrene in the toes of both hind extremities of a male rabbit. An acutely inflamed vein (fig. 7) obtained at biopsy from a man having thrombo-angiitis obliterans had been embedded adjacent to the right femoral vessels.

from the kidney of one rabbit and from the blood of the heart of another. Green-producing streptococci and Micrococcus catarrhalis were obtained in culture from the tonsils of three patients with thrombo-angiitis obliterans. Two rabbits were given intravenous injections, and a third rabbit was given injections in the muscles of the thigh, adjacent to the femoral vessels; the results were negative. The tonsil from a patient with thrombo-angiitis obliterans was embedded between the muscles of the thigh of a rabbit, adjacent to the femoral vessels; the results were negative. Cultures were made from the nasopharynges of two patients with thrombo-angiitis obliterans. One culture was injected into the testis of a rabbit, and the other was injected intravenously; the results were negative. The washings of a swab from an ulcer on the foot of a patient with thrombo-angiitis obliterans were injected adjacent to the femoral vessels of one rabbit; this yielded negative results. Cultures of diplococci from a gangrenous

toe and of indifferent streptococci and Micrococcus catarrhalis from tonsils of patients with arteriosclerosis were injected intravenously into two rabbits. The results were negative, except that diplococci similar to those previously injected were isolated from the bile and kidney of one rabbit. The fourteen rabbits that died lived from four to ninety-six days. One rabbit was killed on the sixteenth day. Sections of the femoral vessels did not contain organisms.

Material was collected from the prostate glands of thirteen patients with thrombo-angiitis obliterans and injected into sixteen rabbits (table 4), in part, as follows: Seven rabbits were given intravenous injections with cultures containing green-producing streptococci associated with either staphylococci or Micrococcus catarrhalis. Two rabbits were given indifferent streptococci. One rabbit was given an injection of 2 cc. of secretion from the prostate gland mixed with gelatin-Locke solution, and two were given injections of green-producing streptococci and Micrococcus catarrhalis in the testis. Thrombosis was not observed, and the sixteen experiments yielded negative results, except for the isolation of green-producing streptococci from the blood of the hearts of two rabbits and from the blood of the heart, liver, kidneys and prostate gland of another rabbit. The twelve rabbits that died lived from one day to two months. The four rabbits that were killed lived from five to twenty-three days.

Comment.—It is obvious that the pathologic lesions found in the vessels of these rabbits were similar to, if not identical with, those found in patients with thrombo-angiitis obliterans, and represent, so far as we are aware, the first lesions of this type that have been produced in animals. Rosenow stated that he has never seen these lesions occur spontaneously in rabbits. It is a question whether the lesion in thrombo-angiitis obliterans is a distinct entity, and, until this is settled, the results of experiments on animals must not be held to be conclusive. We obtained the best results either by injection of the pleomorphic streptococci adjacent to the femoral vessels or by embedding vessels from human beings adjacent to the femoral vessels of experimental animals. Inconsistent results were obtained from intravenous injections of pleomorphic streptococci into these animals. This is in accord with Buerger's experiments, as he obtained positive results only when he embedded acutely inflamed superficial veins from patients with thrombo-angiitis obliterans adjacent to normal vessels of human beings who previously had had thrombo-angiitis obliterans. He obtained negative results in animals. Our study suggests that thrombo-angiitis obliterans is of infectious origin, and that the pleomorphic streptococcus may be of etiologic significance. The presence of a filtrable virus as the causative agent of thrombo-angiitis obliterans, however, must still be considered.

SUMMARY

Acutely inflamed veins and arteries were obtained at biopsy or at amputation of extremities in thirty-four cases of thrombo-angiitis obliterans. Gram-positive, pleomorphic streptococci were obtained in pure culture in nine cases, and green-producing streptococci, in two. Arteries and veins from ten amputated extremities of patients with arteriosclerosis were cultured in a similar manner, and five cultures yielded gram-positive, pleomorphic streptococci. Cultures from normal arteries and veins of twenty-four other patients were negative.

Four different methods were used in attempting to reproduce thrombo-angiitis obliterans in experimental animals: 1. Pleomorphic streptococci were injected intravenously into thirteen rabbits. Intimal proliferation with thrombosis took place in two. Thirty-one rabbits were given injections in a similar manner with organisms obtained from extracted teeth, tonsils, the nasopharynx and secretions of the prostate gland. Negative results were obtained. 2. Pleomorphic streptococci were injected into the femoral muscles, adjacent to the femoral vessels, of forty-two rabbits. Intimal proliferation and thrombosis occurred in ten rabbits. 3. Portions of the vessels obtained from patients with thrombo-angiitis obliterans were embedded in positions adjacent to the femoral vessels of twenty-nine rabbits and one dog. Intimal proliferation and thrombosis occurred in seven rabbits, and in one rabbit trophic changes and dry gangrene developed in the toes of the hind feet. 4. Vessels that had been previously shown to contain pleomorphic streptococci were embedded into the pulp cavities of teeth of two dogs. The results were negative. The results obtained by injecting organisms at sites adjacent to the femoral vessels of rabbits and those obtained by embedding segments of vessels from human beings in positions adjacent to the femoral vessels were essentially the same (23.8 and 24.1 per cent, respectively positive). The pathologic lesions found in the vessels of these rabbits appeared to be identical with those seen in human beings with thrombo-angiitis obliterans, and represent, so far as we are aware, the first lesions of this type that have been produced in experimental animals. The study suggests that thrombo-angiitis obliterans is of infectious origin, and that the streptococcus may be of etiologic significance.

COMBINED CONGENITAL EXSTROPHY OF THE FEMALE URINARY BLADDER AND CLOACA

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CHICAGO

Malformations of the cloaca may be arranged in two groups, depending on the presence and the absence of an associated exstrophy of the bladder. The factors in both are essentially the same. The reports on record demonstrate that the malformations make a transitional series from a patent urogenital sinus to an exstrophy of the bladder with intestinal fistulae in the exstrophied tissues. This discussion is limited to the latter malformations. Previous reports of combined exstrophy of the cloaca and bladder deal chiefly with evidence that the deformity may have offered in explanation of exstrophy of the bladder. Here an attempt is made to correlate the significance of the malformations with the embryologic history of the lower portion of the bowel. Spina bifida, ununited symphysis pubis, epispadias, deformities of the labia and scrotum, undescended testes, ununited müllerian ducts in the female and anomalies of the kidneys and ureters are so often associated with exstrophy of the bladder with intestinal fistulae that they have been considered a regular occurrence by some authors. There are, however, examples without anomalies of the kidneys and ureters or spina bifida.

Anomalies less frequently associated include umbilical hernia, absence of the umbilical cord, retroflexion of the trunk and differences of arterial distribution.

Combined exstrophies of the cloaca and bladder have been known for some time. Förster [1] in 1865 stated clearly the essential features, namely, ununited pubic bones with an exstrophy of the bladder, an opening into the lower portion of the ileum placed centrally in the upper portion of the defect, absence of the colon or presence of a rudimentary colon in the form of a short blind tube with an opening below the one for the ileum, and in the female the persistence of paired and ununited müllerian ducts opening laterally and below. In various reports,[2] essen-

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From the Henry Baird Favill Laboratory of St. Luke's Hospital.

1. Förster: Die Missbildungen des Menschen systematisch dargestellt, ed. 2, Jena, F. Mauke, 1865.

2. Ahlfeld, F.: Die Missbildungen des Menschen, Leipzig, 1880. Sequeira, J. H.: J. Anat. & Physiol. **30**:362, 1896. Shattock, S. G.: Tr. Path. Soc. London **46**:248, 1895. Keith, A.: Brit. M. J. **2**:1857, 1908. Wood-Jones, F.: J. Anat. & Physiol. **46**:193, 1912. Johnston, T. B.: ibid. **48**:89, 1913. von Geldern, C. E.: Arch. Surg. **8**:61, 1924.

tially the same anomalous conditions are mentioned. The explanations of origin differ.

In the reports by Doran,[3] Bryce [4] and Emrys-Roberts and Patterson,[5] the anomalous conditions appear similar to those discussed, but differ enough to be mentioned separately later.

According to Connell,[6] exstrophy of the bladder was first reported in 1595 by John Schenke. The first record of this malformation in the female is by Van Horne, in 1670. Since then, the number of reports has increased rapidly, and many theories have been advanced in explanation of the defect. Förster,[1] in 1865, seems to have been the first to discuss exstrophy of the bladder associated with intestinal fistulae. These malformations are much less common than the uncomplicated exstrophies of the bladder, but the etiology of both probably centers on a common factor. Connell [6] reviewed in detail the theories of exstrophy of the bladder and classified them under three general headings, namely: (1) mechanical, (2) pathologic and (3) due to arrested development. At this time, however, three hundred years since the first case was described, no theory of etiology is universally accepted.

REPORT OF A CASE

A full term female infant was born at St. Luke's Hospital, in the service of Dr. H. K. Gibson, on April 16, 1931. The mother had three healthy living children. The labor was prolonged. There were no deformities of the head, chest or extremities, except a left equinovarus. There were no changes of the heart or lungs. The umbilical cord was 35 cm. long and had a broad base through which the loops of bowel were visible. Below this was a defect of the anterior abdominal wall; from the center of this defect protruded the mucosal surface of an evaginated segment of bowel. Urine and feces passed onto this surface; it became markedly reddened and the edges gangrenous. On April 19, the infant had a fever of 99.2 F.; breathing became labored, and she died the next day.

Only the essentials of the postmortem record are mentioned. The body weighed 2,585 Gm. and was 44 cm. long. There was slight general icterus. The stump of the umbilical cord was dry, and below the base was a dry, tan-brown, tough membrane 7.3 by 3 cm. A huge cleft of the abdominal wall below the umbilicus formed a triangular region 9 cm. wide and 14 cm. long over the curved surface of the distended abdomen. This mass of soft red tissue bulged because of the intra-abdominal tension and was divided into three parts. In the center, a tissue 5 cm. long and 3.5 cm. wide protruded 2.4 cm. and was covered by a glistening mucosa. It was surrounded on each side by a crescent-shaped lateral mass also covered by a smooth, glistening red mucosa. The central bulging portion contained an opening into the ileum. The red lateral masses presumably were the dorsal wall of the bladder. At the bottom of the reddened mass where the edges of the skin united

3. Doran, A.: J. Anat. & Physiol. **15**:226, 1881.

4. Bryce, T. H.: J. Anat. and Physiol. **29**:553, 1895.

5. Emrys-Roberts, E., and Patterson, A. M.: J. Anat. & Physiol. **40**:332, 1906.

6. Connell, F. G.: J. A. M. A. **36**:637, 1901.

in the perineal region was a small bifid, tonguelike mass of tissue, the genital tubercle. Extending upward and laterally the mucocutaneous margin was widened and thickened on each side by a ridge of skin representing the labia majora. An anus, proctodeal depression and spina bifida were not present. The pubic bones were widely separated.

The body was opened by a midline incision extending down to the cleft in the abdominal wall and then laterally on each side to preserve intact the structures concerned with the malformation. The abdominal wall below the umbilicus was less than 1 mm. thick and had no muscle tissue. The liver weighed 150 Gm.; the right lobe in the right anterior axillary line extended 8 cm. below the costal margin to the iliac crest. The left lobe of the liver in the midline was 9 cm. below the tip of the xyphoid process. The small bowel, distended with gas, seemed to have the usual length and was attached by a mesentery in the midline. Several centimeters of the distal portion was adherent to the visceral surface of the evaginated tissues. The small bowel reached the floor of the small pelvis, curved upward, herniated into the bulging mass previously described, and opened to the external surface in the upper portion of the protruding mass. There were two other openings in the central mass. One, 6 cm. below that for the small intestine, entered a blind segment of bowel, 1.5 cm. in diameter and 6 cm. long, attached in the midline in front of the spine by a short mesentery. It had no paired appendages; the other, 1 cm. above the latter, opened into a small appendage having the shape and size of an appendix vermiformis, 2.5 cm. long and 0.3 cm. in diameter. This was coiled along the side of the visceral surface of the bulging mass and was attached there by a thin mesenteriolum. On the external surface, 1 cm. below the inferior margin of the bulging mass, their centers 0.9 cm. from the midline, were the paired openings of cone-shaped appendages, each 4.5 cm. long, 2.5 cm. thick at the base and 0.6 cm. in diameter distally, and ending in a short coiled tortuous tube (fallopian tube). Beneath the end of each tube was a mass of soft, dark red tissue, 1.3 by 0.3 cm., which by histologic examination was identified as ovary. There was no connection between the cone-shaped structures (müllerian ducts). The colon was absent. The kidneys had no unusual features. The ureters entered the pelvis medial to the paired cone-shaped appendages, where they diverged and opened on the lateral masses of tissue 1.5 cm. above and outside of the opening leading into the paired appendages (müllerian ducts). Except for bronchopneumonia there were no other changes elsewhere in the body.

COMMENT

The descriptive anatomy of these combined exstrophies in the reported accounts is essentially the same. There is, however, a difference of opinion regarding the nature of the various structures in this condition. The intestinal openings on the ventral wall of the body were interpreted by Ahlfeld, Keith and Sequeira as the misplaced vitelline duct, an opinion not widely accepted. Ahlfeld thought the misplacement was due to a short umbilical cord, but this explanation does not apply to malformations with a normal umbilical cord.

Some authors considered the malformation a persistent cloaca. The embryologic history of the cloaca supports this view, in that a urogenital aperture corresponding to the upper extent of the primitive cloacal membrane prior to the separation of the cloaca into bowel and bladder

would result in such an anomaly.[7] Johnston [2] and von Geldern [2] attempted to clarify the matter by a histologic study of the tissues. Both identified the lateral red regions as vesical mucosa and the central portion into which the intestines open as large intestine. The mucosa of the upper opening was small intestine. Johnston stated that if a layer of bladder epithelium could be demonstrated, interposed between the normal skin below the umbilical cord and the intestinal mucosa, the cloacal nature of these structures would be established and the contention of vitelline duct participation in the anomaly refuted. Von Geldern was able to demonstrate such a layer of bladder epithelium. In the case now reported, the identification of the lateral red regions as urinary bladder was made by demonstrating ureteral openings in these tissues. The epithelium of these regions had desquamated, and the histologic preparations were, therefore, unsatisfactory. The mucosa of the central bulging mass had fine villi covered with columnar epithelium but no true valvulae conniventes. The muscular layer was well developed; although the sections were bowel wall, they had no distinguishing structures by which to differentiate between small and large intestine.

The central mass anatomically represented a large cecum, with three openings: (1) into a vermiform appendix, (2) into the small intestine at the upper portion and (3) into a blind colon at the base. Sections of the appendix and of the small and large bowel had the usual structure of these tissues. Johnston's specimen had a blind diverticulum that corresponded anatomically to the colon in the case now reported, but did not have tissues of an appendix. The blind diverticulum in Johnston's report had mucosa which, at the distal end, was like that of the large bowel and, proximally, was a transition between small and large intestine. The anomaly described by von Geldern had no structure corresponding to the large bowel, but had paired diverticula that histologically resembled large intestine. They may have been the colon and a large appendix. A structure anatomically corresponding to the colon has been reported by all authors except Emrys-Roberts and Patterson, and Bryce, and a single or bifid appendix vermiformis by all except Bryce and Doran. The histology of these structures was not recorded by the authors. An anomaly in a full-term fetus, described by von Berenberg-Gossler [8] has considerable significance. This fetus had an anal fold, two scrotal sacs, a rudimentary penis but no anus or urethra. The distal loop of the ileum was connected with the vertex and posterior wall of the urinary bladder by a tube (designated X). The cecum with two vermiform appendixes and a short dorsally curved colon end-

7. Arey, L. B.: Developmental Anatomy, Philadelphia, W. B. Saunders Company, 1926, p. 148.

8. von Berenberg-Gossler: Anat. Hefte **49**:615, 1913.

ing blindly was continuous with this tube behind and below. Von Berenberg-Gossler concluded, like Kermauner and, later, Johnston, that the cloaca forms a much larger part of the bowel than is generally believed.

The intestinal tract originally is a straight tube. Subsequently, a marked growth in length occurs. The center of this growth activity, according to von Berenberg-Gossler, is in the cloaca, from which develop the lower portion of the ileum, the cecum, the appendix, the colon and the rectum. This conclusion seems to be supported by the anomalous anatomic relations found in the case here described and other combined exstrophies of the urinary bladder and cloaca.

SUMMARY

Combined congenital exstrophy of the female urinary bladder and cloaca was observed in a full-term child that lived four days after birth.

A plausible explanation for the anomaly assumes that the cecum has a direct anatomic relation with the primitive cloaca and that growth activity concerned with the formation of the lower portion of the ileum, the cecum, appendix, colon and rectum centers in the cecum.

Conversely, the theory proposing such an embryologic process for these intestinal structures is supported by the anomalous anatomic conditions found in the combined exstrophies of the urinary bladder and cloaca.

General Review

THE ORIGIN AND ANTIQUITY OF SYPHILIS: THE EVIDENCE FROM DISEASED BONES

A REVIEW, WITH SOME NEW MATERIAL FROM AMERICA

HERBERT U. WILLIAMS, M.D.
BUFFALO

Concluded from page 814

REVIEW OF ALL REPORTED CASES OF ANCIENT SYPHILIS OF BONE

AMERICA

The first reference to syphilis of bone in remains of American Indians that I have found is in a brief note by Farquharson, dated 1875. In an account of the exploration of mounds near Davenport, Iowa, he said of the skeletal remains: "Evidence of the prevalence of syhpilis was quite common in the form of nodes."

Shortly after this, there appeared the monograph of Dr. Joseph Jones of New Orleans, whose report was of considerable importance and excited much discussion in various parts of the world. The work of Jones will be considered farther on in the present article. Parrot's statements concerning certain skulls from Peru appeared about the same time.

In subsequent years, many other specimens of bones alleged, with more or less confidence, to be both ancient and syphilitic, have been described. For the sake of clarity it seems to me best to consider first the cases that satisfy the two criteria mentioned most completely, rather than to take them up according to their geographic distribution. The specimens in order of importance are: skulls found by Kidder at Pecos, N. M., and described by Hooton; a skull and some long bones found by Tello at Paracas, Peru, and described by Tello and Williams; a skull from the Rio Negro region in Argentina; several long bones from one skeleton found by Kroeber in the Cañete Valley in Peru, now in the Field Museum, Chicago, not previously reported on; long bones excavated by Mills and Shetrone from mounds in Ohio, some of which have, and some of which have not been, previously described; a skull collected by Dr. Joseph Jones, Big Harpeth River, Tenn.

Besides these, there are numerous skulls and long bones from points as widely separated as the middle of the United States and Argentina, many of which are important, though not so well authenticated as the first six lots of specimens.

Skulls from New Mexico.—At Pecos, N. M., extensive excavations of a ruined pueblo have been made by A. V. Kidder for the department of archeology, Phillips Academy, Andover, Mass., beginning in the year 1915.[9] The Spaniards of the expedition of Coronado (1540-1542) found this pueblo inhabited by several hundred people. A diminishing number of their descendants continued to occupy it until 1838. According to Kidder, his excavations passed through a number of superimposed strata, with which he was able to associate various types of pottery.[10] The lowest stratum, belonging to the earliest occupation, was dated as from 800 to 1,000 years ago (Hooton, p. 332).

An enormous amount of skeletal material was obtained by Kidder, which has been described by Hooton, including three specimens strongly suspected of being syphilitic. In Hooton's words (p. 311): ". . . all of them are definitely and indisputably prehistoric." His case 60455 I consider the best piece of evidence now extant for the existence of pre-Columbian syphilis in America. These specimens are all in the Peabody Museum, Harvard University, Cambridge, Mass. The fact that the nasal region is involved in all three cases is probably the result of coincidence; in point of time, the three belong to periods probably one or more centuries apart.

Pecos Case 60455 (skull and right femur from the level "black and white," or "glaze I," therefore very ancient [figs. 18*A*, 19 and 20]): According to Hooton, the skull is that of a middle-aged female. It shows well marked deformation from flattening of the posterior part of the parietal bone and the adjacent part of the occipital bone on the left side, which is common among Indian skulls. It is rather heavy, though not exceedingly so. The enamel of the teeth is considerably worn away by grinding, as is frequent in old Indian skulls; one molar in the upper jaw shows some caries; there is no notching of the two incisors remaining. There is partial destruction of the nasal bones, with subsequent healing; the vomer and turbinates are loose and in large part missing, probably lost post mortem, as frequently happens in these Indian skulls. The most characteristic lesion is shown on the frontal bone, of which the greater part is involved, only the posterior one fifth being exempt. The surface is roughened by the presence of many low, flat elevations, some small, some large, separated by irregularly running, linear depressions,

9. In 1926, during a brief visit, I saw these excavations in progress; even to an amateur it was evident that they were conducted with most scrupulous care.

10. The succession of cultures indicated by the various types of pottery is shown in the following table (Hooton, p. 10):

1. Late archaic: corrugated (little), strong blind corrugated; black on white.
2. Period of the introduction of glaze: strong and medium blind corrugated; glaze I, biscuit A.
3. Period of concentration: faint blind corrugated; glaze II and III, biscuit B.
4. Late prehistoric (?) 1600: featureless black; glaze IV, glaze V, biscuit B.
5. Early historic, 1600-1680: striated black, late glaze V, beginning modern (?).
6. Late period, 1680-1840: striated black (?), plain red, polished black, modern.

frequently stellate and corresponding closely with the description given by Virchow for typical syphilitic lesions of bone (fig. 19). On both sides, the process extends downward as far as the articulation with the malar bone and nearly or quite to the orbit and nasal bones. On the left, near the junction with the malar bone, is a depression with slightly elevated edges radiating from it, indicating a lesion nearly, but not completely, healed. On the right, just in front of the middle, are three more depressions of the same character. The most conspicuous lesion is an area just to the left of the middle, roughly rectangular in form, about 4 by 3 cm., where the external table and diploe have evidently been destroyed by necrosis, while the

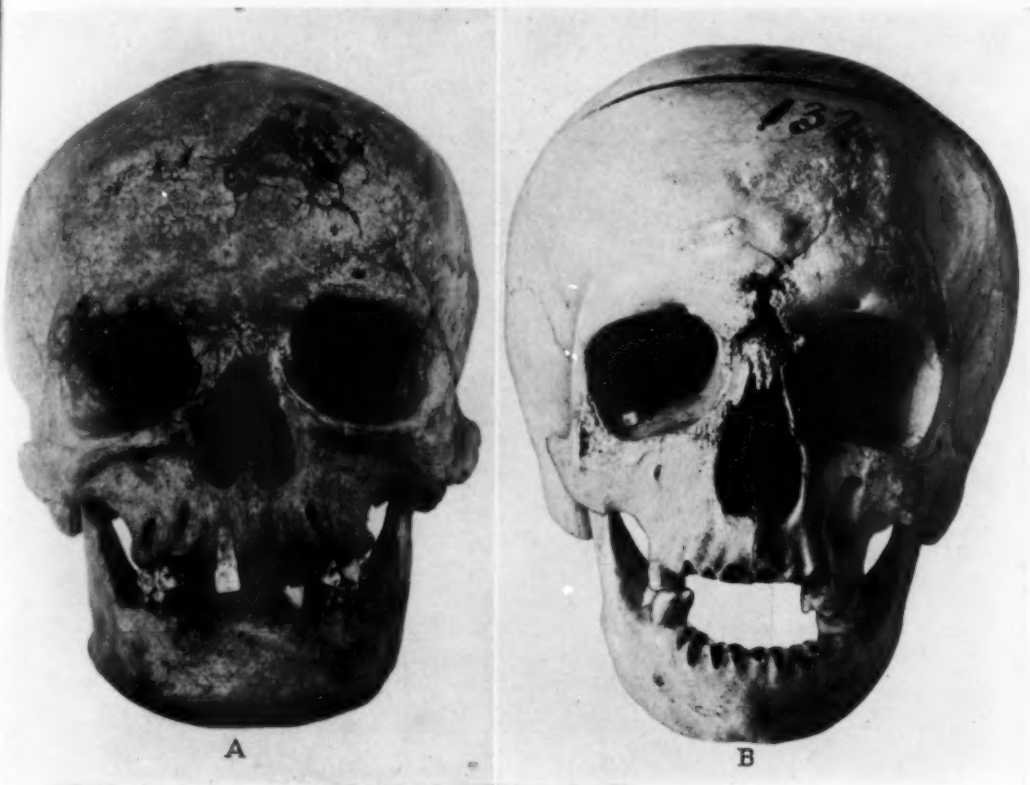


Fig. 18.—*A,* Pecos case 60455. The photograph was furnished by Prof. E. A. Hooton, Peabody Museum, Cambridge, Mass. *B,* the skull in a case of congenital syphilis, Prague. The photograph was furnished by Prof. A. Ghon.

borders are elevated and partly healed. The central part of this area still contains what may be the remnants of a sequestrum. The posterior part of the edges of this area shows fine lines of new-formed bone running in the direction of radii drawn from the center of the whole area. The inner surface of the skull apparently is slightly roughened over a region corresponding to the same area. The right parietal bone has an area, roughly 5 cm. square, but of irregular form, extending from the parietal eminence nearly to the coronal suture, where there are a little

caries and a number of small, stellate scars. Over the left parietal eminence is a smaller area of the same sort, from 2 to 3 cm. in diameter.

I have examined this specimen several times, and in my opinion, if it is possible to make a diagnosis from a dried bone without other evidence, this must be called a syphilitic skull. It so closely corresponds with an old skull in the museum of the German University at Prague on which a diagnosis of congenital syphilis was made (autopsy in 1874 probably by Preitz; no history; girl of 15) that a photograph is introduced for comparison (fig. 18 *B*).

Fig. 19.—Detail from Pecos case 60455.

One has, however, some more evidence in case 60455 in the shape of the right femur (fig. 20), which shows on the inner border a well marked thickening, partly in the lower half of the shaft but rather more in the upper half. Its surface is smooth and rounded. The roentgenogram shows plainly that there is a rather dense bony growth from the periosteum, encroaching slightly on the medullary canal below. A small piece was taken from the posterior surface and sectioned. The microscope showed that it has the structure of a periosteal osteophyte. There are none of the marks of periostitis with osteomyelitis, and the location would be an unusual one for periostitis due to injury. The femur, therefore, makes valuable confirmatory evidence for the syphilitic nature of the disease shown on the skull.

Pecos Case 59864 (skull from the level "glaze II," according to Hooton, from a middle-aged woman [fig. 21]): An ulcerative inflammation has destroyed the

lower portion of the nasal bones and the borders of the apertures. There was perforation of the alveolar borders through the alveoli of the right canine and the lateral incisors. The roof of the palate is cicatrized. There are areas of thickening on the frontal bone, the malars and the orbital walls. There are areas of erosion on the left side of the frontal bone, coming down to the supra-orbital ridge, with irregular

Fig. 20.—Pecos case 60455, right femur (original photograph). The roentgenogram was made by Dr. E. C. König, of the Buffalo General Hospital.

linear scars like those seen in syphilis of the cranium, of which this is in all probability a case.

Pecos Case 59814 (from the level "glaze III" [figs. 22 and 23]): This is a fragment of a skull; according to Hooton, it is from the skull of a young woman. As described by Hooton: "The roof of the palate shows evidence of inflammation and a pathological deposition of bone. The posterior third of the palate is

Fig. 21.—Pecos case 59864. The photographs for figures 21, 22 and 23 were furnished by Prof. E. A. Hooton, Peabody Museum, Cambridge, Mass.

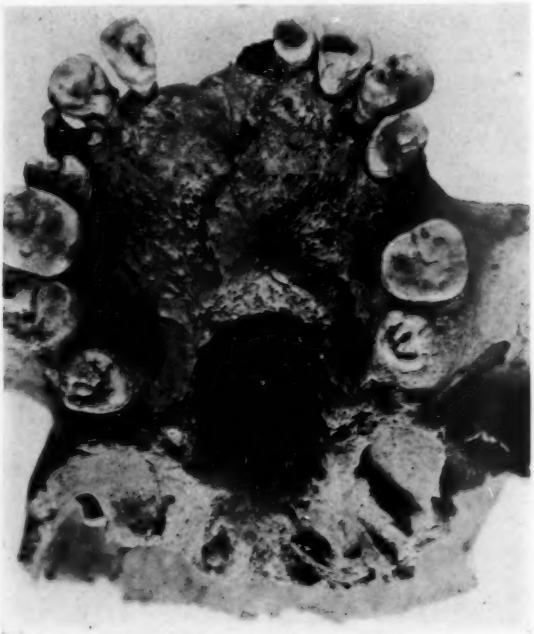


Fig. 22.—Pecos case 59814, perforation and inflammatory changes of the palate.

perforated by a hole almost square in shape, but with corners rounded and with the edges bevelled and cicatrized. This hole is about 2 cm. square. The nasal orifice is a round, cicatrized hole of about the same size as the perforation through the hard palate, with which it is continuous. The borders of the nasal aperture have been covered with a thick, bony deposit which is bevelled inward, and the lower halves of the nasal bones are involved in this cicatrix." The diagnosis in this case is puzzling and in my opinion cannot be made with certainty. The lesion about the nose suggests to me traumatism as a cause, but the perforation of the palate seems very significant on account of the frequency of this lesion in syphilis.

Fig. 23.—Pecos case 59814, cicatrized nasal aperture.

Skull and Long Bones from Paracas, Peru.—The peninsula of Paracas protrudes as a kind of point into the Pacific Ocean, 18 kilometers south of the port of Pisco, which again is about 200 kilometers south of Callao and Lima. The locality is one of exceptional desolation even on that arid and forbidding coast.

Dr. Julio C. Tello, then curator of the Peruvian Archeological Museum at Lima, made explorations that disclosed the presence of curious bottle-shaped tombs, buried below the sand and excavated in a hard clay or shale (Tello, 1929). The tombs contained numerous mum-

mified bodies wrapped in beautifully embroidered cloths. Many of the skulls had been trephined. The characters of the pottery, implements and ceremonial objects led Tello to conclude that the burials antedated the well known Nasca period; others regarded them as indicating a variety of early Nasca culture. In any case, they were much earlier than the Inca period, which began about 1200 A. D. Tello repeatedly found evidence that when the tombs became filled, some of the older bodies were removed to make room for the more recent ones. The bodies thus

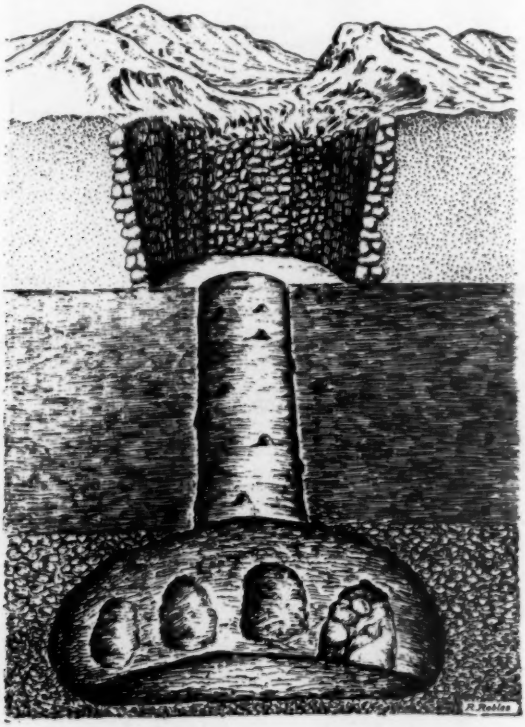


Fig. 24.—A diagram of tomb 5, Paracas, Peru, showing the vestibule above, the cavern below, and the tube that connects the two. This and seven other illustrations of this case are from an article of Tello and Williams (Ann. M. Hist. **2**:519, 1930).

removed were buried around the entrance to the tomb; the specimens of interest to the readers of this paper seemed to belong in the latter category; they were found just outside of the tomb. The condition of affairs is shown clearly in Tello's diagram of tomb 5, which contained forty-eight bodies (fig. 24). The tomb proper opened to the exterior by a tube 1.66 meters in height, with a diameter of 1 meter at the bottom, the upper opening being covered by bones of whale, skins and

mats. The upper opening was surrounded by an enclosure called the vestibule, which was lined with stones and resembled a shallow well. Several skeletons and some other bones were found in the vestibule and in the sand just above it. Two of the diseased bones, a left tibia and a left humerus (case 12-7509), were found in the vestibule. Removal of the sand in the places contiguous to the cavern disclosed other diseased bones, among them the cranium, the two femurs and the ulna.

The skulls found in the Paracas tombs generally showed a peculiar type of artificial deformation called by Tello "cuneiform," produced by pressure on the frontal and occipital bones. Tello found some bodies with the apparatus for deformation actually in position, in principle like

Fig. 25.—Left, a lateral view of the ancient skull from Paracas, Peru, case 12-7509; right, frontal region of same skull. The photograph was made by the American Museum of Natural History through the courtesy of Dr. H. L. Shapiro.

the apparatus advertised by modern "beauty doctors." The skull (12-7509) showed the same type of deformation as in those found in the tombs. This and the long bones presented a dark yellowish-brown patina like old ivory. The cultural objects, among them a plate of gold in the form of a five-pointed star, found with the bones outside of the tomb were of the same kind as those found within the tomb; there were no cultural objects belonging to a later period. While the possibility that the bones under discussion were introduced through an intrusive burial must be conceded, the facts stated indicate that they were of the same age as the bodies within the tomb. The wild and lonely nature of the surroundings also made a recent intrusive burial unlikely.

In November, 1929, I visited Paracas in company with Tello. It was apparent to me that only the person who actually conducted the original excavations was in a position to decide as to the antiquity of the bones to be described. Concerning this, Tello had not the slightest doubt. He is the most experienced archeologist in Peru, having made archeologic exploration in many parts of his country, both in the Andes and along the coast, his life work as is well known to other archeologists and anthropologists.

Fig. 26.—Detail of skull from Paracas, case 12-7509.

The specimens are described in an article by Tello and myself. The illustrations and the descriptions of the bones here are copied from that article. It is not certain that the skull and the long bones came from the same skeleton, but they probably did so. The skull is syphilitic, as far as it is possible to make the diagnosis on a dried specimen without the clinical history.

Skull from Paracas (figs. 25 and 26): The region involved by the disease includes the frontal bone, both parietal bones, the occipital bone and both mastoids. The involvement is most marked on the left side, behind and below, that is, the lower posterior angle of the left parietal bone and the adjacent mastoid bone.

Nearly the whole frontal bone from the ridges of the eyebrows back is affected. The surface presents low elevations, varying in size, but about 1 cm. in diameter, between which are depressions, which, especially on the right side, are frequently linear, sometimes stellate.

The right parietal bone is affected in the same way as the frontal bone, but less notably. Just below the parietal eminence are two minute openings into the interior of the skull; each is situated at the base of a small, depressed scar; they were probably produced by disease. Another small opening a little farther back was probably made post mortem.

The disease appears to have extended on to the right mastoid from the adjacent parietal and occipital bones; the changes here are not marked.

The anterior half of the occipital bone is involved; the irregularity of the surface is not great. At about the middle of the area of involvement occurs a depression, 1.25 cm. long by 2 cm. broad, approximately rectangular in form; it is due to erosion of the external table, probably produced by active ulceration, but possibly formed post mortem.

The surface of the anterior half of the left parietal bone is only slightly irregular; the posterior half exhibits severe involvement. Just behind the parietal eminence is an area of ivory-like, irregular thickening, about 4 cm. long by 3 cm. broad. In the lower posterior half of the parietal bone occur four openings into the interior of the skull. Three of these openings are minute, being 1 to 4 mm. in diameter. All occur at the bottoms of depressed scars. None of them could be due to postmortem erosion. The fourth and lowest opening is larger. Its form is very irregular, something like an ax with a short handle; its greatest length is about 28 mm.; its greatest breadth about 10 mm. Its edges are thin, but rounded. There is no evidence of injury or fracture. It bears no resemblance to the results produced by trepanation, as could be determined by comparison with many admirable examples of trepanation done by the ancient Peruvians in the large collections under Tello's direction. It is evidently the result of ulceration that has healed. Below this opening are five small areas of active ulceration, two on the parietal bone, two on the mastoid bone and one at the junction of the parietal and mastoid bones. Over the lower and posterior part of the parietal bone are about nine irregular, short, linear scars, some of them stellate, corresponding closely in form to the lesion described by Virchow as pathognomonic of syphilis.

The inner surface of the skull is smooth. There is no indication of fracture. The skull is rather heavy. It is moderately flattened anteroposteriorly. The sutures are nearly obliterated. The lower jaw is missing. In the upper jaw, the second right molar, the third left molar and the stump of the first left molar are the only teeth present. The second bicuspid and first molar on the right were lost during life, as was shown by atrophy of the alveolar process. The skull was evidently that of an elderly person.

Long Bones from Paracas (fig. 27): The long bones are two femurs and the left tibia, humerus and ulna.

The right femur is 40 cm. long. It shows well marked thickening at about its middle third on the anterior and outer aspect. The area of thickening is smooth and is evidently a new growth from the periosteum. The left femur is 39.5 cm. long. It is thickened over a part of its anterior and outer aspect, beginning below the great trochanter and extending over about the upper fourth. There is thickening also in front, extending to a point below the middle. The area of thickening is mostly smooth, though it shows some small openings and short vertical grooves. The growth is evidently periosteal.

The angles made by the necks of the femurs with the shafts indicate that the femurs came from an elderly person.

The left tibia is 33.5 cm. long. It presents the most marked involvement of any of the long bones, almost all of it being affected except the region just below the head. It is enlarged, the circumference at the junction of the upper and middle thirds being nearly 10 cm. The surface is slightly nodular and is roughened by having many punctate openings and short vertical grooves.

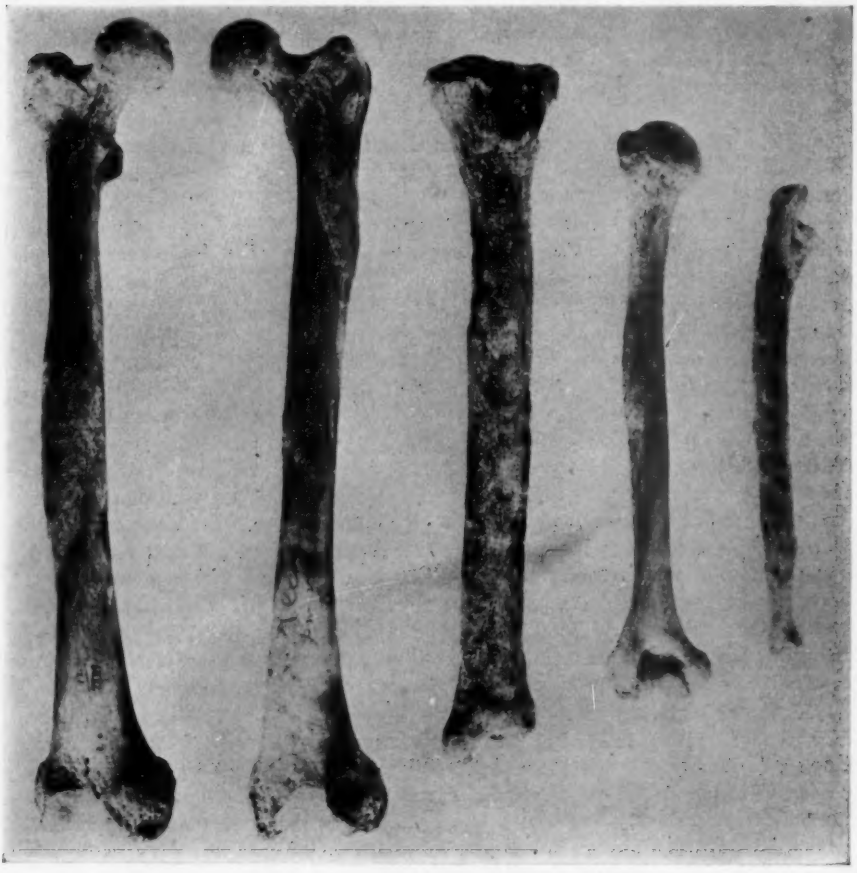


Fig. 27.—Long bones, case 12-7509 (photograph from American Museum of Natural History, New York).

The left humerus is 27.5 cm. long. It is thickened moderately in its upper half, especially in the second quarter from above, where there are many small openings, partly longitudinal. It is not noticeably heavy.

The left ulna is heavy, in spite of the fact that a small portion of the lower end is broken off. The portion remaining is 21 cm. in length. It is thickened throughout its circumference and throughout its length. The surface is slightly nodular and is made still more irregular by many small openings, partly longitudinal,

shown especially at the upper and lower ends. It bears considerable resemblance to bones seen in cases of acute periostitis and osteomyelitis.

The absence of sinuses and sequestrums in any of these long bones may be noted as being in favor of the diagnosis of syphilis and against that of periostitis and osteomyelitis.

An admirable roentgenogram of the long bones was made for us by Dr. Oscar Soto of the Loayza Hospital, Lima (fig. 28). The new growth of periosteal bone

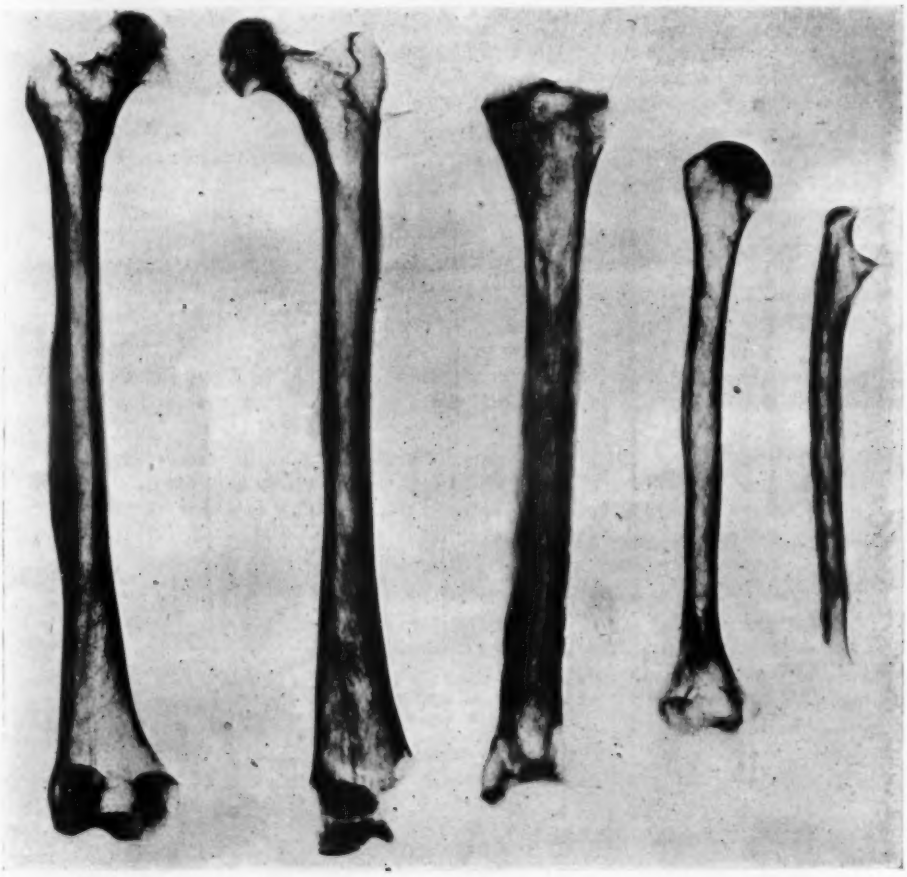


Fig. 28.—Long bones, case 12-7509. The roentgenogram reproduced here was one of the best examples of the roentgenologist's art that I have seen; it has suffered greatly in being reduced in size and in the loss of detail in the process of photo-engraving. It was made by Dr. Oscar Soto, Loayza Hospital, Lima, Peru.

in all of the bones is plainly shown. There is also some encroachment on the medullary canal. The delicacy with which the normal framework of the bones appears in the roentgenogram, especially at the ends of the femurs, is probably due to removal of some of the calcium salts by natural agencies post mortem. In having small pieces of the bones decalcified to make sections for study with the microscope, referred to in a subsequent paragraph, it was remarked that decalcification

with 5 per cent nitric acid was unusually easy and rapid. The x-ray picture is consistent with syphilis; it could have been produced by chronic periostitis and osteomyelitis; it does not resemble that seen in osteitis deformans (Paget's disease).

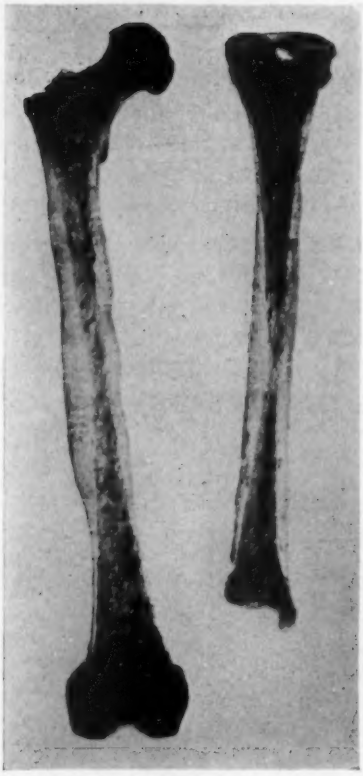
For examination in sections, the right femur and left tibia were sawed through vertically (fig. 29 *A*). The new growth of periosteal bone on the surface is plainly shown. The narrowing of the medullary part of the bone is especially marked in the tibia. The evidence given by the roentgenogram is therefore confirmed and amplified.

After the right femur and left tibia had been sawed through, pieces were removed from the most thickened parts. In 5 per cent nitric acid, they were easily and rapidly decalcified. Sections were made after fixation in formaldehyde and embedding in celloidin. These were stained with hematoxylin and eosin; the hematoxylin was practically without effect. The outer surface stained more deeply with eosin than the inner parts (fig. 29, *B* (femur) and *C* (tibia). The cavities occupied by the bone cells were visible, but not distinct. Foreign material was plentiful, especially in or near the outer surfaces. It consisted of dark particles, evidently soil, threadlike masses and small round bodies that were derived from some unidentified fungus, and large, generally rounded, yellow masses that could not be identified.

The sections show that both bones consist of layers of lamellae, which are deposited very irregularly near the outer surfaces. Both show numerous cavities of considerable size, running in general parallel with the long axes and with the outer surfaces. The line between the new-formed periosteal bone and the underlying bone is well marked in the section from the femur; in the section from the tibia, the line is less distinct. In general, the structure agrees with the descriptions given for syphilitic long bones. The large size of the spaces appears to me to indicate the presence of osteitis as well as of periostitis; this view is in agreement with the encroachment on the medullary part of the bone shown in the roentgenograms and in the longitudinal sections. Haversian systems, poorly developed, appear in both sections in small numbers near the outer surfaces. In my opinion, the sections from the Paracas bones indicate the presence of an osteoperiostitis that was probably caused by syphilis, though possibly produced by some other cause. One can state confidently that, in any modern museum of pathology, these bones would be regarded as syphilitic. All of the roentgenologists to whom I have shown the original plate after bringing it to the United States have agreed on the diagnosis of syphilis.

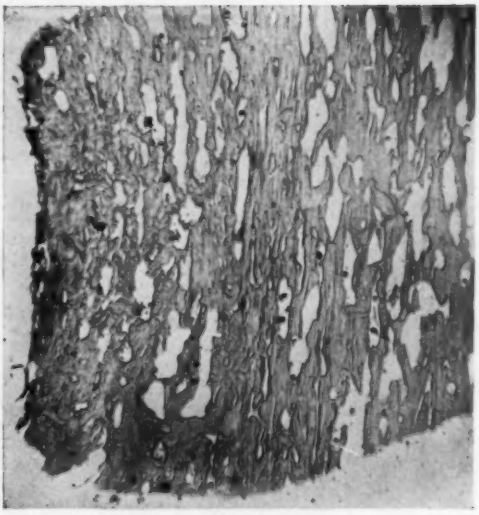
Other Material: A large amount of material from Paracas remains to be examined. It is a most promising field for future study.

In November, 1929, I saw a mummy (no. 262) unwrapped by Tello that proved to be of much interest. The body was immediately surrounded by many yards of cotton cloth and finally some cloths embroidered in colors, among which were a few flat, crude gold ornaments and other cultural objects. The knees were flexed against the body. The arms lay over the abdomen. The anterior abdominal wall was intact. Practically none of the soft structures below the middle of the thorax could be identified. The body had evidently been subjected to heat, even to the point of burning. The bifurcation of the trachea,



A

B



C

Fig. 29.—*A* shows the right femur and the left tibia, case 12-7509, after being sawed; *B*, a section of the femur (magnified about from 6 to 7 times); *C*, the tibia (magnified about from 6 to 7 times). (Original photographs.)

the trachea, the larynx and the esophagus, and the parts above them, were well preserved; all were rather dilated; the aorta was not found.

A pathologic condition of much interest was discovered on the roof of the mouth in the form of an ulcer, 26 mm. long and 24 mm. wide, roughly oval, near the median line (fig. 30). It formed a dark, depressed area, from which the mucous membrane had been removed. There was erosion of the bones of the hard palate, with a small perforation just back of the center of the ulcer. The edges of the ulcer were sharply defined. Dr. Pedro Weiss, of the Loayza Hospital, prepared films and sections on the ground. I also brought tissue from the edge of the ulcer and some of the tarry material on its surface

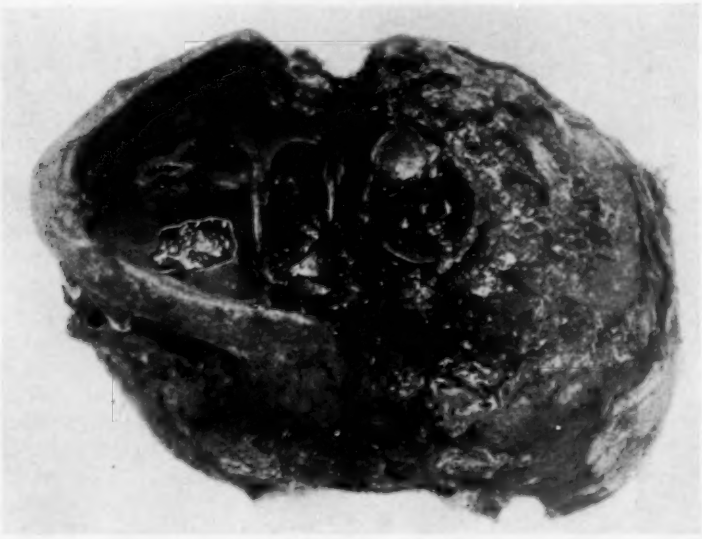


Fig. 30.—Paracas mummy 262. The skull, seen from below. An ulcer of the hard palate is shown. The illustration is enlarged from a small photograph, somewhat retouched (original photograph).

away with me, in the faint hope that spirochetes might be found. However, none were demonstrated either by the Levaditi, Fontana or india ink method; study of the structure with the microscope yielded nothing important. No evidence of syphilis was seen in the nasal or other bones. Some fragments of blood vessels, probably arteries, were obtained from the axilla; no evidence of disease could be detected in them. Nevertheless, I feel certain that the first thought of a physician of the present day, on seeing such an ulcer, would be of syphilis. With fresh material, he could probably make an exact diagnosis.

Rio Negro Skull from Argentina.—This specimen was presented at a meeting of the Society of Anthropology of Paris in 1880 by Moreno

(along with another cranium) as an example of a very ancient skull. It had lain at a depth of nearly 4 meters in a layer of sandy, yellowish clay that formed the ancient alluvium of the river that enters the Atlantic Ocean about 6 degrees south and somewhat west of Buenos Aires. It was believed to be from the glacial time of Patagonia, which is more recent than the glacial periods of Europe. The discussion by the members of the society indicated that some of them had doubts of the skull being of so high an antiquity. Hrdlicka (see bibliography in fourth reference), who visited Rio Negro, I believe, about 1910, after examining the locality came to the conclusion that: "In view of the facts presented above, it seems that the two 'fossil' Patagonian skulls have no solid claims to geologic antiquity, the probability being strong that these crania belonged to relatively recent Indian occupants of the region."

I understand that his opinion that the crania were probably those of relatively recent Indians is to be interpreted in a geologic sense, and does not signify that they may not have been pre-Columbian. Hrdlicka said that he did not see the crania in question.

Lehmann-Nitsche said that the pre-Columbian origin of the skull is unquestionable. The specimen is in the museum of the National University at La Plata, Argentina, catalogue number 781. (Lehmann-Nitsche, the well known anthropologist, now of Berlin, was for many years director of the division of anthropology in this museum.) I regret that I have not been able to secure an original photograph of the skull. The illustrations published in the articles mentioned hereafter are not clear enough to permit me to form an opinion.

At the meeting in Paris referred to, the skull was pronounced to be syphilitic by Bordier, Bertillon (Senior) and Broca.

Stegmann wrote a report on the specimens showing disease of bone in the museum at La Plata, in which an account of this skull was included, with a poor illustration. The skull was fragmentary; the face and base and half of the left parietal bone were missing. In certain lesions, beginning above the ridge of the left eyebrow and extending backward, there was evidence of injury, and there might have been traumatic osteomyelitis. The location of the disease process in general, and its appearance, spoke strongly for syphilis. Tuberculosis could be excluded, but on account of the importance of the specimen in medical history, especially that part of it where there was evidence of injury, traumatic osteomyelitis must be considered.

Lehmann-Nitsche brought this skull with him to Germany in 1904, and von Hansemann described it at a meeting of the Berlin Society for Anthropology. He agreed with Stegmann that there had probably been an injury to the left side of the frontal bone, although the lack of any change corresponding to it on the inner surface made that somewhat doubtful. Von Hansemann described the upper surface of the skull as being irregular throughout, with little elevations and depressions that were like scars, except on part of the frontal bone. The scars had smooth edges, well developed near the bregma, diminishing forward, where they no longer appeared to have healed and had rough edges, and perforation had occurred at the

glabella, and nearly so at some other points. The inner surface was for the most part unaffected. No suppurative condition would have produced such smooth scars in bone and such hyperplasia of bone. Tuberculosis, tumor, leprosy and actinomycosis were excluded. Von Hansemann made an unqualified diagnosis of syphilis.

Four Long Bones from One Skeleton, Undoubtedly Pre-Columbian, from Cañete Valley,[11] *Peru.*—The specimens were loaned to me for study by the Field Museum of Natural History, Chicago (catalogue no. 169664), through the kindness of Dr. Berthold Laufer, curator of anthropology. The excavations were made by Dr. A. E. Kroeber, of the University of California, in 1925 (Capt. Marshall Field expedition; see Kroeber, 1926). Dr. Laufer said:

> Number 169664 was obtained from Tomb 2, Site A, at Cerro del Oro, Cañete Valley. It was found associated with no pottery or other objects that might assign it to any period; however, the whole site consists of sixteen burials which are, without exception, of the Proto-Nasca type. It is impossible to fix an actual date, but this period dated from somewhere between A.D. 500 and A.D. 1000, probably nearer A.D. 500 than A.D. 1000.[12]

Neither the roentgenograms nor the sawed bones nor the microscopic sections give the pictures to be expected in Paget's osteitis deformans. One is evidently dealing with a chronic inflammatory process, an osteoperiostitis. At certain points, the process is still active, while over large areas it has subsided after having produced much dense, ivory-like bone. That accounts for the unusual weight of these bones. The involvement of four long bones, the distribution of the process over the entire shaft in three, and the absence of sequestrums and of deep sinuses tend to exclude nonsyphilitic periostitis and osteomyelitis. A probable diagnosis of syphilitic osteoperiostitis therefore seems warranted.

The surface of the skull in this case showed no roughening; its sutures were obliterated; it was much flattened anteroposteriorly; such deformation of the skull was common in Peru. The bones involved were the left femur, the two tibias and the left fibula; the other long bones were not remarkable. The involvement of the left fibula was confined to an area about 5 cm. in length at its lower and inner surface, where there were moderate roughening and thickening, evidently periosteal and corresponding to an area of marked roughening and thickening on the left tibia. No illustration of the fibula is given, on account of the slight amount of involvement. The photographs reproduced here show the external surfaces of the left femur and the two tibias; also each of these bones after it had been sawed lengthwise, with its roentgenogram beside it. Photomicrographs of the sections are also given.

The left femur and the tibias are noticeably heavy. The left femur (fig. 31) weighs 435 Gm.; the right, 275 Gm. A femur from another, but normal, ancient

11. Opens into the Pacific ocean, about 130 kilometers south of Lima.

12. This information was contained in a letter from Dr. Laufer.

Peruvian skeleton, and that of a somewhat larger person, weighs 383 Gm. The length of the left femur is 39 cm. It is slightly curved forward. The entire surface of the shaft is involved, from the lesser trochanter nearly to the knee joint. The shaft is much roughened behind, evidently from new growth of bone. The front is more uniformly thickened and shows numerous stellate superficial scars.

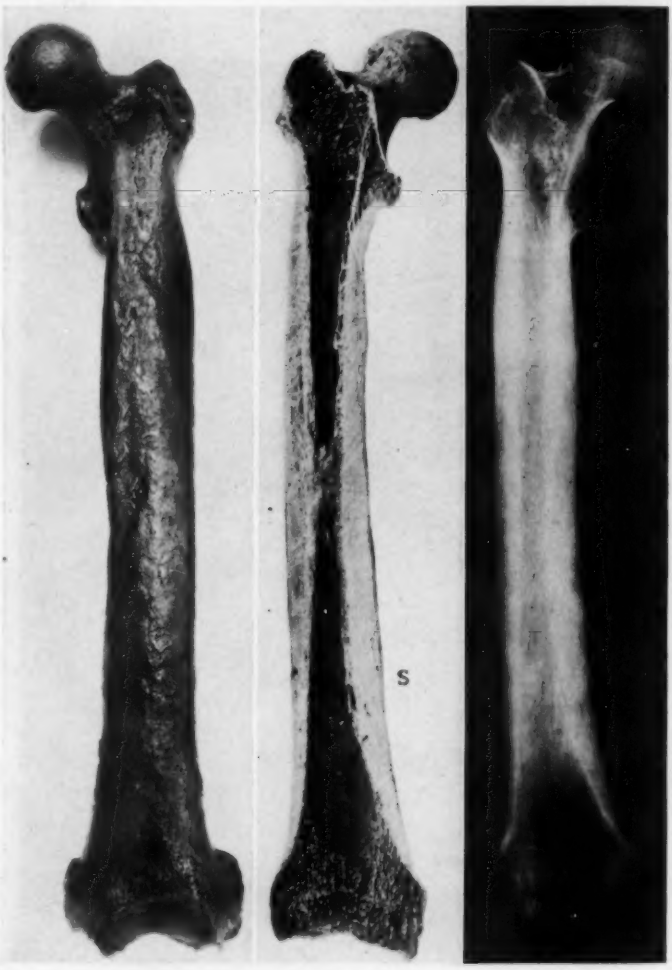


Fig. 31.—The left femur (anterior surface), with the vertical section and the roentgenogram, Field Museum 169664. This femur and the bones shown in figures 32 to 36, as well as some of the photographs and roentgenograms, were loaned to me by the Field Museum, Chicago. All the bones are from a prehistoric skeleton excavated from the Cañete Valley, Peru. *S* indicates the point at which a section was taken for microscopic examination (see fig. 34).

The lower part of the anterior surface looks porous, showing many pointlike perforations. The femur (and the same holds true of the other bones) was sawed longitudinally with great difficulty on account of the dense, ivory-like character of

the tissue. The thickening is most marked along the middle of the shaft. Apparently all layers of the bone participate. There is some encroachment on the medullary canal, but there is still greater new growth of periosteal bone. It is noteworthy that the architecture of the interior of the bone is perfectly preserved, well shown in the cancellous bone at the extremities; but the lamina that separates the lesser trochanter from the rest of the head is unusually thick and is as dense as ivory.

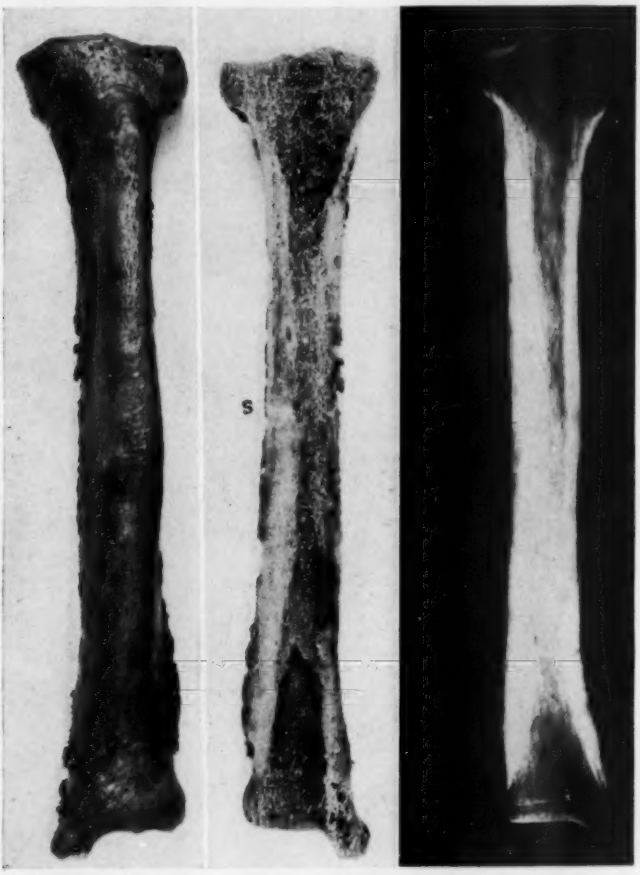


Fig. 32.—The left tibia (anterior surface), the vertical section and the roentgenogram, Field Museum 169664.

The right and left tibia are much alike. Both measure 33 cm. in length; both are heavy. The left (fig. 32) weighs 350 Gm., and the right (fig. 33), 364 Gm. They are decidedly enlarged anteroposteriorly, as is shown where the right tibia was sawed through on that plane, measuring 5.5 cm. at the junction of the upper middle third. In both tibias, the greater part of the outer surface is involved, except that part near the knee joint. There are many osteophytic deposits, evidently periosteal in origin, while the general surface shows large areas punctured with fine openings. In general, the inner surfaces are somewhat more involved than the outer. Both tibias show on their inner surfaces three or four irregularly

defined areas of erosion, which are superficial, extending into the bone to a depth of from 2 to 4 mm. and giving the impression that some process, probably inflammatory, was still actively at work. At other points, the process was quiescent and had terminated with the formation of dense, ivory-like bone. As in the case of the femur, the structure of the cancellous bone at the ends is beautifully preserved, and it has normal architecture. Periosteal new bone formation is plainly shown on

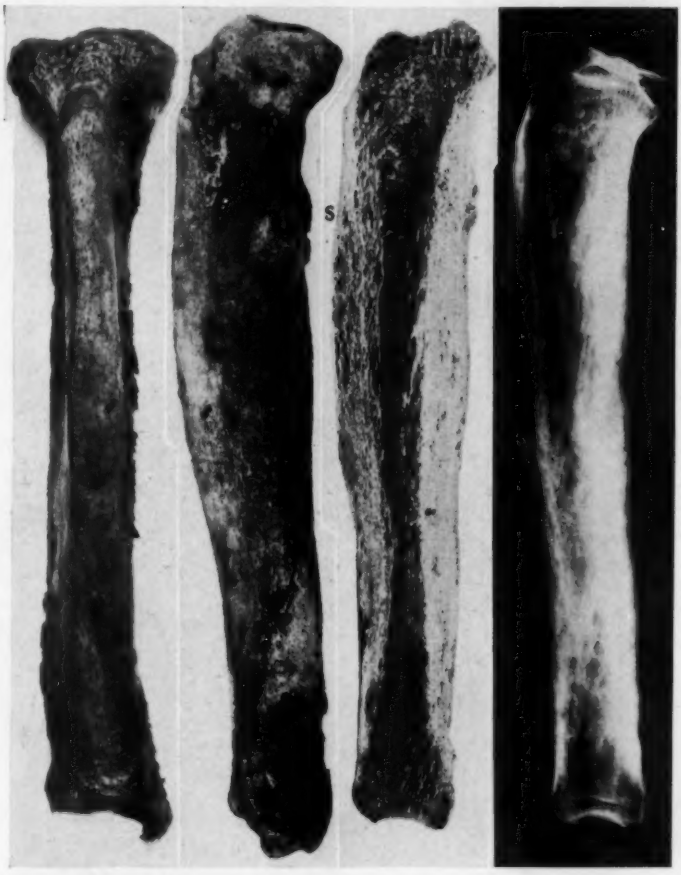


Fig. 33.—The right tibia (anterior and lateral surfaces), the vertical section and the roentgenogram, Field Museum 169664.

the inner side of the left tibia near the point *S* on the sawed bone. In both tibias there is some encroachment on the medullary portion of the bone. The new formation on the outer and posterior part is dense and ivory-like, while the inner and anterior parts are more spongy. The spaces of this spongy bone are large, from 1 to 2 mm. in diameter, and run parallel with the long axis of the bone. No sequestrums and no sinuses leading deep into the bone are seen.

A section of the femur (fig. 34) shows a thin layer of periosteal lamellae parallel with the surface and a projecting osteophyte. Sharpey's fibers can be seen. Haversian systems come close to these lamellae. They show slight irregularity in

Fig. 34.—A section of the femur, Field Museum 169664, after decalcification and hematoxylin-eosin staining; × 12. (Original photograph.)

Fig. 35.—A section of the left tibia, Field Museum 169664, after decalcification and hematoxylin-eosin staining; × 12. (Original photograph.)

distribution, possibly mosaic structures. I should call this somewhat irregular bone formation from osteitis.

A section of the left tibia (fig. 35) was taken at a point below the entrance of the nutrient artery shown in the illustration of the sawed bone; that included in the photomicrograph is therefore chiefly periosteal in origin. However, it consists of well formed haversian systems chiefly, which are regular in their distribution. They come close to the superficial lamellae, of which there is a thin layer parallel with the surface; at one point, not shown in the illustration, the superficial lamellae are deficient. What appears to be the line of the original periosteal surface of the bone appears at the right of the middle of the photomicrograph (Sharpey's fibers can be seen in torn lamellae at this level).

Fig. 36.—A section of the right tibia, Field Museum 169664, after decalcification and hematoxylin-eosin staining; × 12. (Original photograph.)

In the right tibia (fig. 36), at points, a few periosteal lamellae running parallel with the surface are seen. They are not continuous. Moderately dense bone with well developed haversian systems comes close to the surface. Below this is rather loose cancellous bone, with its spaces running longitudinally. The general impression given is that of a regular structure.

All of these sections are made from pieces cut in the long axis of the bone so as to preserve the gross appearance as well as possible. The points from which they are taken are indicated on the photographs by the letter *S*. All were prepared by decalcification, embedding in celloidin and staining with hematoxylin and eosin. No nuclear stain has been secured in any case. Numerous large and small particles from the soil and what are probably spores of molds and other undetermined

foreign materials are found not only on the surface, but in the deepest parts of the sections of bone.

Long Bones of Mound Builders of Ohio.—The earliest reference to the possible occurrence of syphilis in ancient Indian bones from Ohio that I have encountered is in the excellent article of Landon, 1881. He described the diseases shown in bones from the prehistoric cemetery at Madisonville, Ohio. He suggested the possibility of syphilis being the cause of some of the lesions encountered, such as hyperostosis, exostoses and evidence of osteitis. Some lesions were bilateral on the tibias. He gave some fair drawings. Landon did not treat of this aspect of his subject at great length, and he took a reasonable position.

Certain diseased bones found at Baum village in Ohio were described by Orton. The implements and other objects from this locality were pronounced by Mills to be pre-Columbian and to belong to the Fort Ancient culture. The bone specimens were studied at the University of Pennsylvania under the direction of Charles H. Frazier and Allen J. Smith. They consisted of eight tibias, one clavicle and an external cuneiform united by bony ankylosis to the third metatarsal; the last was considered to be due to arthritis. The diagnosis of syphilis was made chiefly on the occurrence of the disease in long bones exposed to injury and on the simultaneous occurrence of rarefying and condensing osteitis. Ground sections of six tibias were examined with the microscope. One of these (no. 7) apparently might have been from a case of Paget's osteitis deformans or of some other condition causing rarefaction of bone. The periosteal formation of new bone in several specimens, especially in Orton's no. 9, seemed to be the feature that was the most convincing for syphilis, sinuses and sequestrums being absent. A probable diagnosis of syphilis for some of the specimens was apparently justified, as far as that is possible for single long bones.

Others of the Mound Builder bones from Ohio were described in 1925 by Means, whose conclusions were based exclusively on the gross appearances and the roentgenograms. Means believed that he was the first to use the x-rays for the study of disease in ancient bones. He said: "Definite gross and roentgenological evidence of syphilis was found in three skeletons. They presented varying degrees of involvement from a simple periosteal thickening and roughening on the crest of the tibia, to thickened ivory-like bone invading the medullary canal with gumma formation. . . . The tibias were involved in all three individuals, in one case both, in another one, the more advanced case, a tibia and ulna." He saw several other more or less suspicious specimens.

Means' article is accompanied by excellent reproductions of his roentgenograms. Two of his specimens are among those described in the present article on the pages directly following (cases 1 and 2).

I have seen the clavicle that is shown in Means' plate I, no. 4, and the roentgenograms of it, and I doubt the correctness of the diagnosis of syphilis for this particular bone.

On April 2, 1931, I had the privilege of seeing a large number of ancient Indian bones at the Ohio State Museum, Columbus, Ohio. The director, Dr. H. C. Shetrone, loaned me some of these bones so that they might be examined more closely; all of them were believed by Shetrone to be prehistoric. Specimens were selected from about fifteen individuals, only those bones being taken that offered good promise of being syphilitic. The roentgenograms were submitted to three different roentgenologists, and only those cases were used in which they agreed that the condition was a new growth of bone resulting from periostitis or osteoperiostitis in all probability due to syphilis. In accordance with these tests, nine of the fifteen cases were pronounced to be, in all probability, syphilis. Seven of the nine cases were from prehistoric Mound Builders (four of the Fort Ancient culture, two from the Gartner site and one from burial no. 4, mound 2, Hopewell). The remaining two of the nine cases were from prehistoric Iroquoian sites in northern Ohio (Tuttle site and Taylor site, each one).

It is certain that the bones that I have seen are only a portion of the ancient diseased, probably syphilitic, bones that have been disclosed by the investigations of the Ohio State Museum, but it is probable that they represent the most striking specimens found in recent years. It is impossible in this article to reproduce photographs, roentgenograms and sections from all the nine cases referred to. Six tibias from four of the cases have been selected as illustrative of the whole group. After they had been roentgenographed, they were sawed vertically and small bits were taken for examination with the microscope. Three of the tibias are apparently the same as three of those described by Means.

We have, then, the authority of one of the most modern and the most experienced investigators of Mound Builder remains (Shetrone) for the statement that the bones just described are prehistoric. The gross appearance of these bones, especially after they have been sawed, shows new periosteal growth of bone. In some of them, the new growth of bone encroaches on the medullary canal. This is confirmed by the examination with the roentgenogram and the microscope. The condition seems not to have been the result of Paget's osteitis deformans, but to have been due to periostitis. The absence of sinuses and sequestrums is against a periosteal growth in connection with infectious osteomyelitis. The extent of the process in all of these bones is against periostitis due to simple traumatism. The results favor a diagnosis of syphilis as far as that is possible in the case of dried long bones without other evidence. The occurrence of lesions in both tibias in two of the cases is also in favor of a diagnosis of syphilis.

Case 1.—Right Tibia, Fort Ancient Culture, Ohio State Museum No. 52 (Figs. 37 and 38): This seems to me to be one of the specimens described by Means (his number 1, plate 1). The length is 39 cm.; the weight, 240 Gm. The area of involvement includes about one half of the length of the shaft, coming somewhat nearer the upper end than the lower end. The enlargement over this area is

Fig. 37.—Long bone of a prehistoric Mound Builder, Ohio, Fort Ancient Culture. The right tibia (anterior surface), the vertical section and the roentgenogram (by Dr. E. C. König, Buffalo General Hospital) are shown. (Case 1 from Ohio, this article.) (Original photographs.)

notable; it comes to an end abruptly at about the beginning of the lower third. Near the upper end is a small group of osteophytes (not very well shown in the photograph). In general, the surface of the area of involvement is rather smooth, except that it is perforated by many small openings for vessels, most of them run-

ning longitudinally. After sawing, the section of the bones shows a dense, ivory-like thickening, evidently periosteal in origin, along the outer border. The inner border is more thickened than the outer (1.5 cm.), consisting of mostly cancellous bone encroaching slightly on the medullary canal. Through the center of this area of thickening runs a lamina of denser bone (not shown well in the photograph) that appears to mark the original outline of the shaft, so that about one half of this new growth is periosteal in origin. The periosteal nature of the new growth is shown in the roentgenogram. The architecture of the medullary portion of the bone near the extremities is well preserved and perfectly normal.

Fig. 38.—A ground section of the tibia (× 12) in case 1 from Ohio, this article. (Original photograph.)

Case 2.—Right and Left Tibias, Fort Ancient Culture, Ohio State Museum No. 46 (Figs. 39 and 40): This seems to be one of the cases described by Means (his number 2, plate 1). The bones are badly broken. They feel light and are friable, as though most of the organic matter had been lost. The photographs show that one of them cracked badly in the process of sawing. Both of these tibias present thickening on the anterior aspect; the inner and outer surfaces are involved in each case. The thickening, which is slightly nodular, involves the upper two thirds of the shaft, coming close to the head. The surface is, in the main, smooth and rounded, but is beset with innumerable well marked grooves running in the long axes of these bones; the grooves presumably carried blood vessels; in some places there are fine, punctate openings. In the sawed bones, the periosteal nature of the

thickening is evident; this also appears distinctly in the roentgenograms. The medullary canal is large. The architecture of the cancellous bone at the extremities, as far as it has been preserved, appears normal.

Case 3.—Left Tibia, Fort Ancient Culture, Ohio State Museum No. 78 (Fig. 41): The length of the bone is 41 cm.; the weight, 254.5 Gm. Slightly more than the lower two thirds of the bone is involved along the anterior and inner surface. Thickening of the bone becomes notable about the junction of the lower and middle third; the photograph fails to represent this thickening adequately. Near the middle of the region of the thickening, over an oval-shaped area about

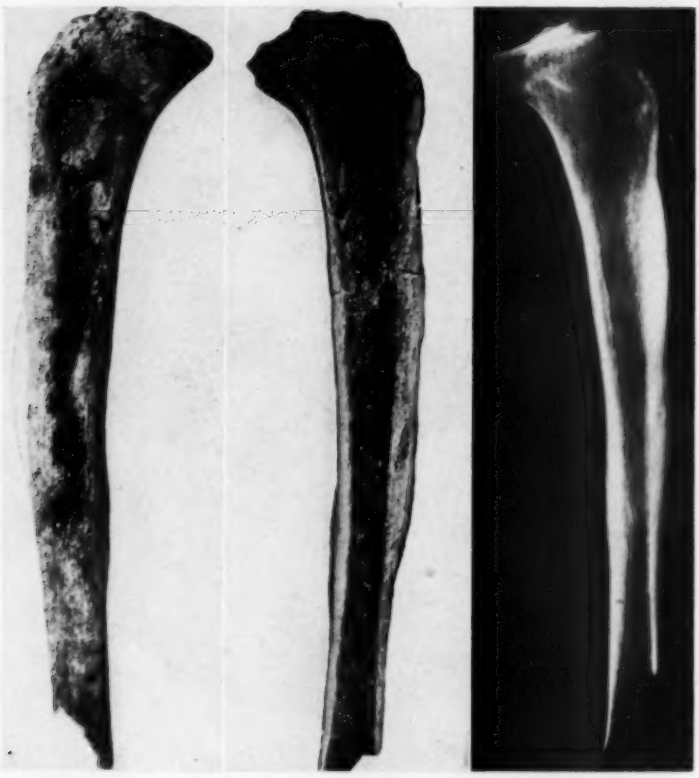


Fig. 39.—Long bone of a prehistoric Mound Builder, Ohio, Fort Ancient Culture. The right tibia (anterior surface), the vertical section and the roentgenogram are shown. The left tibia in the same case is shown in figure 40. This is case 2 from Ohio, this article. (Original photographs.)

4 cm. in length, the surface is perforated with a multitude of minute openings (this could represent an active gumma). The surface of the shaft over a considerable area above the malleolus is very irregular from the formation of osteophytic growths with numerous small perforations; there is some formation of osteophytes along the posterior and inner border in the upper part of the shaft. In general, the upper part of the area of involvement is smooth, except for fine lines running longitudinally. The roentgenogram and the longitudinal section of the bone show

thickening along the anterior border. This thickening apparently is chiefly from periosteal growth with some participation also of the osseous tissue below. The new growth of bone is fairly dense, but that toward the interior of the shaft is in part cancellous. The medullary part of the bone toward the ends displays a perfectly normal architecture and is well preserved.

CASE 4.—Right and Left Tibias, Burial No. 4, Mound 2, Hopewell, Ohio, State Museum, No. 589 (Figs. 42, 43 and 44): Both tibias are 36 cm. in length; the left weighs 156 Gm., and the right, 158 Gm. Both of these tibias present along the

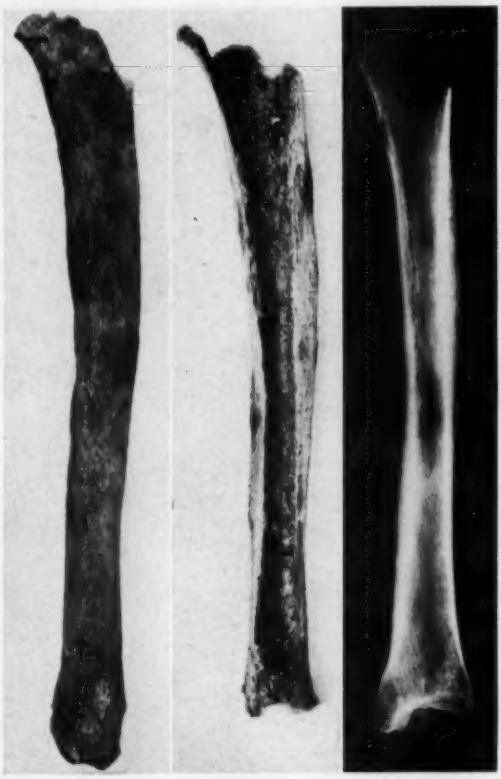


Fig. 40.—The left tibia of the same Mound Builder as was the right tibia shown in figure 39 (case 2 from Ohio, this article). The roentgenograms of both tibias were made by Dr. E. C. König, Buffalo General Hospital. (Original photographs.)

anterior borders, about the middle of the shaft, nodular thickenings with smooth and rounded surfaces, on the right 6 cm. and on the left 10 cm. in length. The surface of the bone over these areas shows many punctate or linear depressions, evidently for the transmission of vessels. The roentgenograms and the sections, after the bones had been sawed longitudinally, demonstrate that the thickening is almost wholly periosteal; the architecture of the medullary part of the bone at both ends is normal.

As sections in cases 1, 2, 3 and 4 made by decalcification proved unsatisfactory on account of the small amount of organic matter remaining in the bones, sections were made by grinding, with fairly good results. The points from which they were removed are indicated on the photographs by the letter *S*. All of these were photographed under

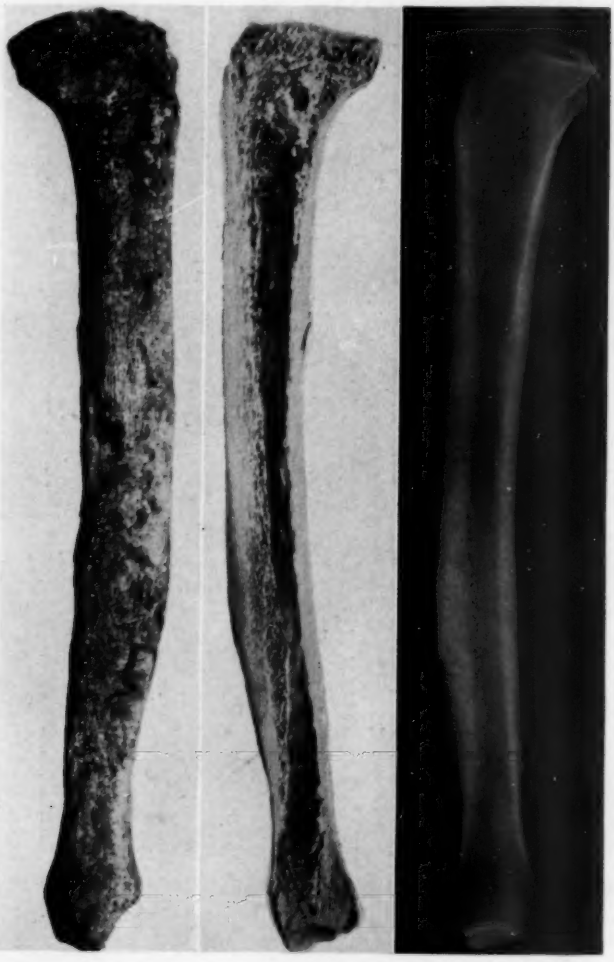


Fig. 41.—Long bone of a prehistoric Mound Builder, Ohio, Fort Ancient Culture. The left tibia (anterior surface), the vertical section and the roentgenogram (by Dr. E. C. König, Buffalo General Hospital) are shown. This is case 3 from Ohio, this article. (Original photographs.)

low power magnification; only two of the photographs were reproduced, as they represent the conditions prevailing in all four cases (figs. 38 and 44). All sections were made in longitudinal direction. The minute

structure was badly preserved. The lacunae for the bone cells could not be identified. In general, it could be said that the new growth of bone consisted of laminae running parallel with the surface. The line marking the junction of the new growth of periosteal bone with the underlying bone of the shaft was usually plainly seen, though not more so than

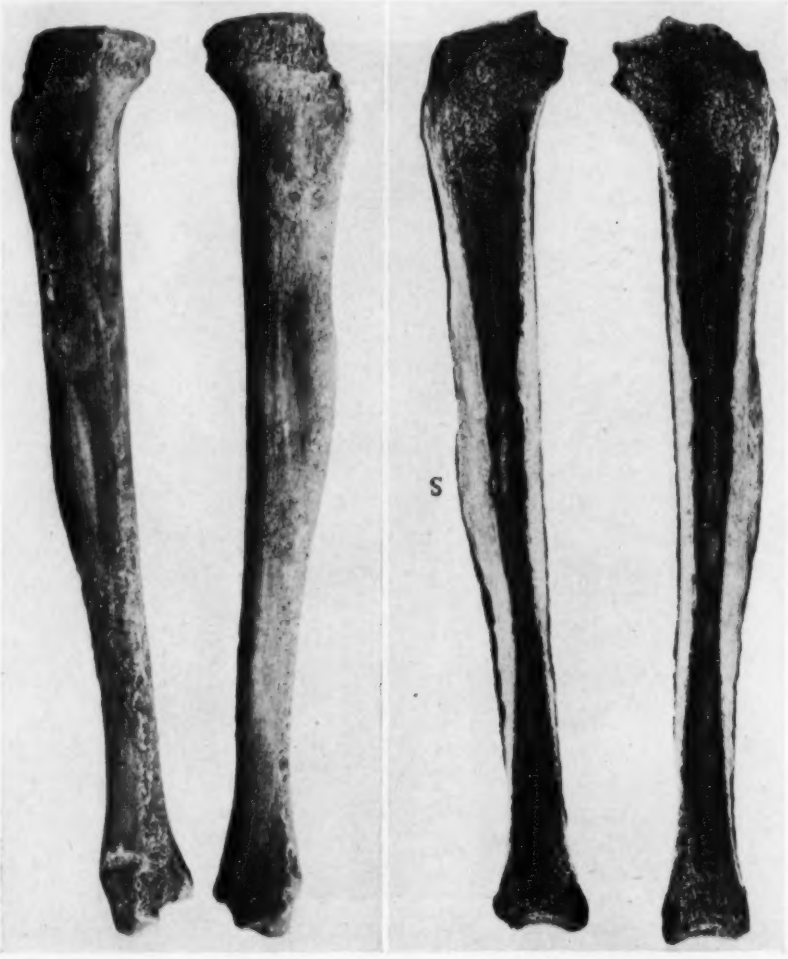


Fig. 42.—Long bones of a prehistoric Mound Builder, Ohio, Hopewell mound no. 2. The right and left tibias (anterior surfaces) and the vertical sections are shown. This is case 4 from Ohio, this article. (Original photographs.)

in the gross specimen. In general, the impression given was that the new layers of bone were of rather regular formation. In case 1, the organic framework of the outer layers had apparently been dissolved out and the substance later on infiltrated with mineral salts, doubtless

calcium. These layers were divided into small polygonal areas, traversed by fine fibers, which dissolved in acid, but which we were not able to analyze with the polariscope. The spaces for the blood vessels often contained yellowish masses, apparently derived from blood. No red corpuscles could be recognized. This substance appeared in all of the sections examined. There was only a small amount of foreign material.

Fig. 43.—Roentgenogram of tibias in case 4 from Ohio. This was made by Dr. E. C. König, Buffalo General Hospital.

Bones from Stone Graves in Tennessee.—The first to make a serious attempt to demonstrate the antiquity of syphilis in America was Dr. Joseph Jones, professor of chemistry and clinical medicine in the medical department of the University of Louisiana. Jones published a monograph on his studies of Indian remains obtained from explorations of stone graves and mounds in Tennessee, chiefly from the point of view

of an archeologist. The amount of skeletal material that he excavated was apparently not large. Nevertheless, he encountered several skeletons that seemed to him to show evidences of having been affected extensively by syphilis, the exact number of such skeletons or of the individual bones involved not being clear from his text. The number of diseased bones for his total skeletal material was surprising.

No illustrations of the bones in question were given. From the descriptions it appears to me that some, if not all, of these bones were syphilitic. As to the age of the remains, Jones said that they could not be less than from one hundred and seventy-five to two hundred years

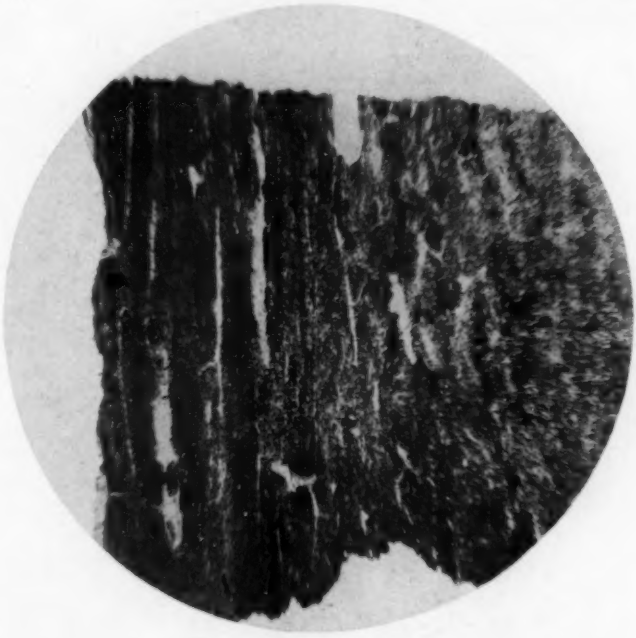


Fig. 44.—A ground section of the right tibia (× 12) in case 4 from Ohio. (Original photograph.)

old (in 1876), and that they might be much older (Jones' article, pp. 50, 72 and 175). No implement of European manufacture was found associated with them, he stated, and no metal, except copper, which was, of course, used by the Indians long before the arrival of Europeans. It is possible, however, that the graves and mounds in question were made after the whites came on the ground. Considering that Jones' article appeared more than fifty years ago, his work impresses me as having been well done.

Bloch collected comments on this material. Virchow remarked that the description of the bones did not indicate that "they must be syph-

ilitic." Putnam (an archeologist, not a pathologist), who examined the specimens, said that the disease affecting these bones might be something other than syphilis; he does not say that they were not prehistoric. Klebs, who also saw these bones in 1896, said that "they showed unmistakable syphilitic bone disease." Jones' descriptions of the bones alleged to be syphilitic are given in the excerpt from his article which follows (see also article by Brühl, listed in the bibliography). The only

Fig. 45.—A skull from Stone Grave, Big Harpeth River, Tenn., described by Joseph Jones. The photograph was furnished by the Museum of the American Indian, Heye Foundation, New York City, by the courtesy of Dr. Bruno Oetteking.

skull from Jones' collection that I have been able to trace is probably syphilitic, as will be shown in a later paragraph (fig. 45).

Referring to mounds on the Cumberland in Tennessee, Jones (p. 49) stated:

> Several of the skeletons in these mounds bore unmistakable marks of the ravages of syphilis. In one skeleton, which appeared to manifest in the greatest degree the ravages of this fearful disease, the bones of the cranium, the long bones

of the arm (the humerus, ulna and radius) and the long bones of the thigh and leg (the femur, tibia and fibula) bore deep erosions, nodes and marks of severe inflammatory action. Many of the long bones were greatly thickened, presenting a nodulated, eroded and enlarged appearance. When sections were made they presented a spongy appearance with an almost complete obliteration of the medullary cavities. The specific gravity of the bones was diminished and the microscopic characters were in all respects similar to those of undoubted cases of constitutional syphilis, which I have observed in my hospital and civil medical practice. Every competent medical observer to whom these bones have been submitted has concurred in the view that syphilis is the only disease which could have produced such profound and universal structural alterations.

Referring to the mounds on the Big Harpeth River, Tennessee, Jones (p. 65) said:

Towards the northern boundary of the mound, in a stone grave immediately at the foot of the two principal graves and at right angles with them, a skeleton was found with the head towards the setting sun. The long bones are strongly marked with syphilitic nodes. The skull is in a good state of preservation, and presents the general conformation of the crania of this ancient race. . . . This cranium had several indentations and nodes on the bones, as if they had been acted upon during life by the syphilitic virus. The external table of the frontal bone appears to have been especially affected. The superciliary ridge is very rough and nodulated, and the nasal bones are thickened, roughened and rounded. The occipital bone shows the effects of pressure which is more marked in the right parietal protuberance, it being much fuller and thrown farther back than the left. The upper extremities of the occipital bone are separated by the transverse suture about one inch in length. (This is possibly the skull that I have seen; Williams, fig. 45.)

I have shown by careful observations that bones taken from stone coffins and burial mounds at Nashville, Franklin, Old Town in Tennessee, and at Hickman in Kentucky, bear unmistakable marks of the ravages of syphilis. The supposition has been advanced that these bones presented merely "traces of periostitis," which were not due to the action of syphilitic poison because "it is uncommon to find shin bones of adults belonging to races clad in skins, and with the lower extremities exposed, in which there is not more or less roughness or hyperostosis along the tibial shafts." So far from these evidences of the action of syphilis being mere traces of periostitis, and constituting mere "roughness or hyperostosis along the tibial shafts," the bones are in many instances thoroughly diseased, enlarged and thickened, with the medullary cavity completely obliterated by the effects of the inflammatory action, and with the surface eroded in many places. These erosions resemble, in all respects, those caused by syphilis, and attended with ulceration of the skin and soft parts during life. Furthermore, the disease was not confined to the "tibial shafts"; the bones of the cranium, the fibula, the ulna, the radius, the clavicle, the sternum, and the bones of the face exhibited unmistakable traces of periostitis, ostitis, endostitis, caries, necrosis, and exostosis. The medullary membrane was evidently involved in many cases to an equal degree with the periosteum; the difference in the appearance of the products of the syphilitic disease being due most probably to the great quantity of fat and other loose tissues, among which the vessels of the medullary membrane run. When thin sections of these bones were carefully examined with the naked eye, and by the aid of magnifying glasses, portions were found resembling cancellous tissue from the enlargement and irregular erosions of the haversian canals, and increase in the number and

size of the lacunae; whilst other portions presented the hardened condition known as sclerosis. I observed in these bones, and especially in those of the cranium, the various forms of osseous ulcerations which have been described by pathologists as characteristic of the action of syphilis, viz., rounded ulcerations with glazed surfaces, and with marked hardening or eburnification of the bone beneath; tuberculated ulcerations, dependent not only on periosteal deposit, but upon chronic inflammation of the compact tissue itself; reticulated ulcerations in which a network of periosteal deposit had been formed, and which had been perforated by ulcers, subsequently forming and assuming the annular type. That these diseases of the bones were not due to mechanical injury, or to exposure to the cold is evident from the fact that they were almost universally symmetrical in their manifestations; thus, when one tibia was diseased the other was similarly affected, both as to the position and nature of the disease. In like manner both fibulae presented similar evidences of periostitis, ostitis and exostosis; this was true also of the bones of the forearm (radius and ulna) and of the clavicle.

The symmetrical distribution of the effects of disease on the two sides of the osseous system could only have resulted from the action of a poison introduced into the blood, and distributed through this medium to all parts of the body.

(Other references similar to these are on Jones' pp. 61 and 85.)

Through Dr. C. W. Duval, of New Orleans, and Dr. S. Bayne-Jones, grandson of Dr. Joseph Jones and professor of bacteriology in Rochester University, it was possible to trace part of the collection of Dr. Joseph Jones to the Museum of the American Indian, Heye Foundation, in New York City. By permission of Dr. Bruno Oetteking, curator of physical anthropology in this museum, I was able to examine the skulls in the Jones collection, and among them found one (fig. 45) that perhaps is the specimen described in the foregoing paragraphs (Jones', p. 65); none of the long bones was identified. In my opinion, the case was probably one of syphilis, though not syphilis of the most severe degree.

The skull is large, heavy and well preserved. It shows some deformation and has the cranial capacity stated by Jones. There are fourteen teeth in each of the jaws, all in good condition, not notched, evidently those of an adult. The coronal suture is nearly obliterated. The most marked lesions are in the lower half of the frontal bone, on both sides of the middle line, where the surface is uneven and porotic, and shows about five stellate scars with depressed centers and elevated edges. There are also two or more scars of the same character on the left side of the frontal bone, all plainly shown in the photograph. It did not impress me that there were changes in the nasal bones.

Other Specimens from America.—Tennessee: Putnam described a mound in Tennessee certainly more than one hundred and fifty years old (in 1877) where there were two hundred and fifty burials from which he obtained parts of fifty-four skeletons. He said: "Several bones collected in this mound show the effects of disease of some kind, and are such as would generally be called syphilitic; but several pathologists who have examined them unite in stating that they do not

prove the existence of syphilis as other diseases than syphilis might leave such effects."

I believe that these bones are still in the Peabody Museum, Cambridge, Mass. Apparently they are among those referred to in two articles of Whitney, who took a conservative position.

Florida: Certain bones, now in the Army Medical Museum, Washington, D. C., excavated by Clarence B. Moore, of Philadelphia, were the subject of an article by Lamb. According to Lamb, the results of Mr. Moore's work had been published by the Academy of Natural Sciences, Philadelphia, the specimens under discussion coming from a mound named the "Lighthouse Mound," described in Moore's "Additional Mounds of Duval and Clay Counties," Florida, 1896, pp. 24 and 25. It was situated on the north side of St. Johns river at Fernandina, Nassau County, Florida. Lamb quoted Moore as follows:

> Exclusive of loose bits of bone, doubtless from the previous excavation, 74 skeletons, all seemingly in anatomical order, were met with and one deposit of charred and calcined human remains. We are, of course, unable to estimate the number of skeletons thrown out or carried away prior to our visit. The first interment was encountered 10 feet in from the southwestern margin of the base. With very few exceptions no art relics lay with the human remains; and if we except a stone hatchet found with a skeleton 8 feet from the surface, and some beads of shell with another interment, no art relics were associated with burials in the body or on the base of the mound.
>
> In no previous work have we found so great a percentage of pathological specimens as in this mound, and, as has not been the case in other mounds, entire skeletons seemed affected, and not one or possibly two bones belonging to a skeleton. The pathological conditions were so marked and cranial nodes so apparent that, in view of the fact that no objects positively indicating white contact were discovered in the mound, though the utmost care was exercised by a trained corps of assistants, we are compelled to regard the bones with the greatest interest since, evidence of contact with the whites being wanting, we must look upon these bones as pre-Columbian in origin. We may state here that all the bones preserved by us came from the depths in the mound which insured their derivation from original burials. These bones found 8 to 12 feet from the surface, and lying beneath numerous undisturbed layers are unmistakably of as early an origin as any yet described and much more reliable than most.

Concerning the specimens, Lamb said:

> The bones were at first temporarily, afterwards permanently, deposited in the United States Army Medical Museum in this city (Washington). They are numbered 11,247 to 11,253, Pathological Series, and 3579 to 3583, Provisional Pathological. They consist of the humeri, right ulna, radii, femora, tibia and fibula. They are of the usual dark color and quite friable; the medullary cavity is filled with dark sand and rootlets. There is some platycnemism and pilasterism, conditions so commonly found in aboriginal bones. They show in some places irregular patches of flat, reticulated, hyperostotic growth, in others a more uniform rounded thickening. The illustration shows the appearance of the left tibia and fibula; the ulcerative stage is well marked. The skull was not sent and its condition is not

now known. In the present state of our knowledge I know of no disease except syphilis in which a series of bones of the same skeleton show the lesions illustrated and described. These bones were exhibited by me in the Pathological Museum at the meeting of the British Medical Association at Montreal, and a brief mention of them was made in the British Medical Journal, November 20, 1897, page 1487. Professor Osler's remark on seeing the bones was that "This man had the pox."

(Lamb's article is accompanied by a fair drawing.)

In April, 1931, I visited the Army Medical Museum and, through Major Callender and Major Ash, was able to examine the specimens deposited in the museum by Clarence B. Moore. The bones described by Lamb were immediately located under the catalogue numbers given by him, and his drawing and description proved to be in general accurate. Roots and sand were still present in the femurs. Places where the left fibula and left femur were broken showed that the new growth of bone was periosteal in origin. The condition of the bones was poor and did not seem to warrant examination with the x-ray or under the microscope. It was my opinion that they were in all probability syphilitic. It seemed somewhat doubtful that the bones could be regarded as certainly pre-Columbian, although archeologists have had a high regard for Moore's work.

The Army Medical Museum contains a quantity of other bones bearing the name of Clarence B. Moore and called "prehistoric syphilis." Apparently they had not been carefully studied and it would be difficult, if not impossible, to prove their antiquity at this date. They are from localities in the southern states. There are some six skulls, only one of which seems to me very suggestive of syphilis, and more than seventy long bones. Many of the latter belong in sets coming from one skeleton. The bones suspected of being syphilitic show irregular thickenings of the shaft; some have a good deal of erosion. The lesions in a few of these may be from osteomyelitis; some may be traumatic in origin; in general, the lesions give the impression of being largely due to syphilis. In view of the new material constantly coming to light, which archeologists are now better able to date accurately than was possible when Moore was at work, it is doubtful that it is now worth while to study his material The large number of bones probably syphilitic that he found in one region is noteworthy.

The Army Medical Museum has at least three skulls of Indians that are in all probability syphilitic, no. 7427 from Maryland, no. 11,535 from Kentucky and no. 12,815 from Alaska. None of these has any note on the label referring to its antiquity.[13]

13. Specimen 9667 is stated to be a "skull of a prehistoric Aleut of Chernoffsky, Alaska, collected by Dr. W. H. Dall, Smithsonian Institution." One can be as sure as is ever possible in the case of a dried specimen that this skull is syphilitic. It is to be regretted that it is not now possible to determine whether or not the skull is prehistoric with equal certainty.

In his report on skeletal remains from Arkansas and Louisiana, Hrdlicka (1909) referred to numerous long bones and a few skulls showing inflammatory changes that might have been due to syphilis.

New Mexico: A cranium was excavated at Mitten Rock by Earl H. Morris for the American Museum of Natural History, which now has the specimen (catalogue no. 99-8518). It was described by Shapiro as an example of prehistoric trephining of very ancient date, pre-Pueblo or post-Basket-Maker. The bones were fragile and badly broken but were beautifully repaired in the museum. The skull was not deformed.

> The opening made by the operation of trephining, roughly circular, about 50 mm. wide and 40 mm. long, included most of the lower part of the right half of the frontal bone. On its left border below, it entered the frontal sinus. The edges were clean-cut with no signs of repair. It appeared to me that there was a small fistula at the root of the nose near the middle that probably led into the frontal sinus and that might have been the motive for the operation. The entire vault of the skull was rough from nodules and depressions of moderate thickness and depth. The surface was also finely roughened throughout, apparently from erosion with partial scaling; at many points erosion still seemed to be active. There may have been a few perforations, though this was somewhat uncertain on account of the damaged condition of the skull. The cranial bones were thin and fragile.
>
> The case is evidently one of periostitis involving almost the entire upper surface of the cranium. Periostitis in this situation and of this extent would usually be attributed to syphilis, but the skull has not the typically syphilitic appearance. However, I have a recent undoubtedly syphilitic skull, the upper surface of which is like this specimen; but in my case the bones are rather thick. On searching for causes that might have produced nonsyphilitic periostitis over such a large area, it occurred to me that scalping or a severe burn, the Indian perhaps being intoxicated, might leave a large area of ulceration that would be months in healing, if it healed at all, and that would undoubtedly affect the periosteum beneath. However, this may well be an atypical example of syphilis of the cranium.

Arizona: The Hemenway expedition to the Salt River valley, Arizona, 1887, brought back a considerable collection of skeletal material, which was preserved and studied in the Army Medical Museum by Dr. Washington Matthews. In his report, he said:

> In several cases the condition suggested the possibility, but by no means demonstrated the certainty, of syphilitic disease. Thus in one there was irregular nodular hypertrophy of the shafts of both tibiae, more especially the right, of the lower part of the right fibula, and of the shafts of both ulnae, while the sternal ends of the first ribs showed exostotic growths. In some cases there was hypertrophy of the tibial shafts without any other evidence of disease. The fragmentary and worn condition of the skulls interfere with the recognition of disease and injury.

Colorado: An excellent paper on pre-Columbian syphilis in America was published in 1891 by Hyde. After reviewing the historical aspects of the subject, he described several bones that might be syphilitic, and

offered some photographs. The author seemed himself to be in doubt that the specimens were surely pre-Columbian, and his descriptions and his illustrations do not indicate that they were surely syphilitic. He concluded that syphilis probably existed in America before the arrival of white men, but that proof from bones that were both ancient and syphilitic was not at hand at the time of the writing of his article.

This paper has an additional interest in that Hyde sent to Prudden two diseased tibias that had been given by archeologists, not named, as being from Colorado, and that antedated the Cave Dwellers (Basket Makers?). Prudden's name has been mentioned by several writers on ancient syphilis in America, but as far as I can learn, the report that he sent Hyde, included in the same article, is his only published utterance on this subject. From Prudden's account of these bones, given with characteristic detail and clearness, it is evident that he saw one of the types of bone lesions that have attracted the attention of many observers and that have been illustrated by various examples in this paper. Prudden gave an excellent drawing of a low power microscopic view of the surface of one tibia, showing that the thickening was due to irregular growth of bone that still had recognizable haversian systems. He concluded that the disease was a rarefying and formative osteitis and periostitis that might have been due to syphilis, but he seems to have inclined to the view that it was due to some other cause.

Hyde contributed an article to Morrow's "System of Genito-Urinary Diseases" (1894) that covers about the same ground as the paper just cited. In the second article, he gave illustrations of a skull, the clavicles, femurs and fibulas of a skeleton from Colorado, furnished by Prof. F. W. Putnam, Peabody Museum, Cambridge, Mass. They seem to be the same as those referred to in his first paper. He gives an excellent very low power photomicrograph of a section of one tibia that shows evident periosteal thickening. The photographs of the gross specimens do not permit one to form an opinion. This plate from Hyde is reproduced in D'Arcy Power and Murphy's "System of Syphilis" (vol. 2, plate 2, London, 1908).

Mexico and Central America: Michäelis gave a brief description of a femur, furnished by Hans Virchow from the collection of the department of anatomy of the University of Berlin, said to be from a Toltec grave, and of a date around 1200-1300 A. D. From the gross appearance of the bone and from the evident periosteal origin of the new-formed bone, he regarded the case as probably syphilitic. His illustrations are not clear, but as far as one can judge from them, his opinion is justified (Michäelis, pp. 52-53, plate XXXII).

Gann, who had had an extensive experience in examining Maya ruins, told of a burial mound opened by him in British Honduras, containing a badly preserved skeleton and certain clay figures. The latter seem to indicate the performance of some operation on the penis, and one of them represents a penis, natural size, having three longitudinal incisions extending the length of the upper surface of the glans.

Of the skeleton, the shaft of the right tibia "instead of being triangular, was rounded in section, the prominent angles at the front and sides being obliterated;

it was slightly bowed, with the convexity anteriorly, and it was a good deal enlarged, especially in its upper two thirds, which were composed chiefly of friable, spongy cancellous tissue which rendered the bone much lighter than it appeared. The surface was exceedingly rough, especially in the upper part of the bone, being covered with a number of small nodular outgrowths between which were small pits or depressions. The bone was not examined microscopically. Of the left tibia only small fragments remained but as far as could be judged from these a change somewhat similar to that undergone by the right bone had also taken place here, though not to such a marked extent."

Gann believed that the image of the penis in pottery was intended to represent disease of the organ in the person whose skeleton had been buried, and who had been an example of pre-Columbian syphilis.

Ricketson mentioned a femur in which the "nubbly appearance" of the shaft closely resembled the lesions of a very virulent disease like syphilis.

Peru: Parrot described three skulls, believed to be ancient, coming from Peru, as showing ancient syphilis. The age of the specimens does not seem to have been proved. From the descriptions it would seem that they probably were from cases of symmetrical osteoporosis of the cranium and not of syphilis.

Ashmead (1894-1895) described briefly a skull from Pachacamac, Peru, said to be in the Bandelier collection of the American Museum of Natural History, New York City (he gave no catalogue number). He stated that the specimen was pronounced undoubtedly pre-Columbian by Saville and by Putnam. He said:

In the right supratemporal region of the skull, on the frontoparietal suture, implicating both bones, there is a mark of disease one and a half inches in diameter. The bone is cancellated, eburnated, with deep corrugations as if eaten by disease; the tissue is almost eaten through. . . . To my mind this is an instance of syphilis in a pre-Columbian skull.

It is not possible to determine from Ashmead's description whether or not his conclusion was justified; he gave no illustration. Also, one may question whether or not a pre-Columbian date could be assigned to the specimen with as much certainty as Ashmead indicated. At the present moment, this skull cannot be located in the collection of the American Museum of Natural History.

In the Bavarian National Museum at Munich, Jäger found no less than twelve skulls from Peru on which he made the diagnosis of syphilis. Six of these were from Pachacamac and four from Ancón (both on the coast not far from Lima); for two, the locality was not stated. Apparently all were regarded as ancient, but no facts in proof of their age were cited. The descriptions of the specimens are not convincing that syphilitic lesions were present in a single one of them. For skull 6, Gaffron Collection, a photograph and roentgenogram are

given, from which I should think that the case was one of symmetrical osteoporosis (cribra parietalia). In any event, the work is without value for the purposes of this study, in the absence of accurate data to determine the age of these skulls.

The skeletal material described by Tello in his monograph, "Syphilis in Peru" (1909), is said to be deposited in the Warren Museum, Harvard Medical School, Boston. I have examined the Tello collection and am not convinced that any of these specimens is surely syphilitic.

The skeletal material collected by the Yale Peruvian expedition, 1912, at Machu Picchu on the eastern side of the Andes, to the north of Cuzco, was described by Eaton. The material was said to be, for the most part, probably pre-Columbian, but some of it might be post-Columbian. Eaton described a femur and several tibias that very probably presented, at least in part, syphilitic periostitis. He gave excellent photographs and roentgenograms; some of these were reproduced in Moody's "Paleopathology." The skull of a child was described by Eaton as giving evidence of necrosis that might have been due to syphilis or to some other cause.

The skeletal material collected by the Peruvian expedition of Yale University and the National Geographic Society in 1914 and 1915 was examined by MacCurdy (1923).

The cranium of a child from Paucarcancha showed a considerable area of necrosis, chiefly on the left parietal bone, with one small point of perforation. MacCurdy made a diagnosis of probable syphilis, but as no new formation of bone was mentioned, I should think that was doubtful. Another cranium of a child from Patallacta had a circular area of necrosis on the left parietal bone, 4.2 cm. in diameter, which had advanced through the skull. Here also, a diagnosis of probable syphilis was made, but no new formation of bone was described. The cranium of an adult from Patallacta had a circular area of necrosis, including the right frontal and parietal bones, 4.8 cm. in diameter, which was chiefly in the external table, but which showed a perforation of the skull near the center over an area 8 mm. in diameter. There was a small scar on the left parietal bone. From the photograph (MacCurdy's plate XLI) I should think that this might well have been a case of syphilis. MacCurdy referred to a considerable number of long bones from the same region that might well have been examples of syphilitic periostitis. He gave excellent illustrations of all his specimens.

In regard to their antiquity, MacCurdy said: "Whether syphilis existed in the New World prior to the discovery by Columbus cannot be settled by the collection under study here. Some of the burials in the highlands of Peru were evidently post-Columbian." All of the specimens referred to came from points in the Urubamba Valley north of Cuzco.

Hrdlicka, in 1913, collected an enormous number of bones in Peru (see Hrdlicka, third reference). Except for one skull, which was very likely modern, he did not mention any bones showing evidences of

syphilis. Apparently he encountered a considerable number of cases of periostitis and osteoperiostitis in long bones of the coastal region in the north of Peru; he gave no suggestion as to their causation.

Argentina: Other probably syphilitic bones have come from Argentina. Their age cannot be determined so definitely as that of the skull from Rio Negro, described on a previous page. They come from the valley of the Chubut River, which enters the Atlantic around 8½ degrees south and somewhat west of Buenos Aires. Lehmann-Nitsche said that the excavations were made by an untrained person, before his own arrival in South America. A large number of graves were opened, and a quantity of skeletal material was obtained; the cultural objects were identical with those of native sources, with nothing of European origin. The culture was the same as that described by Verneau in "les Anciens Patagons" from the same territory, which no one doubts was pre-Columbian.

A skull from the forementioned material, which I understand is in the Museum at La Plata, Argentina, was reported in the article of Stegmann.

> His description of a surface eaten or gnawed, in some spots depressed and in others having elevations and deposits, ridges, warts and so on, seems to indicate that the skull was typically syphilitic. The disease involved the right frontal and parietal bones, passing on to the left side of the frontal bone and to the parietal bone to a smaller extent. The inner surface apparently showed erosions but no new deposits; the diploe appeared to be involved also, as though by a gummatous process. Stegmann seemed clearly to be inclined to a diagnosis of syphilis, but regarded infectious osteomyelitis as not entirely excluded. The illustrations that he gave appear like those of a typically syphilitic skull. I have not been able to procure an original photograph of this specimen.
>
> Stegmann also described two tibias from the valley of the Chubut, of which he gives illustrations. He made a diagnosis of multiple gummatous osteomyelitis. He described nodes, thickenings and fistulas leading to the inner part of the bone. One of these tibias was afterward submitted to von Hansemann, who positively rejected the diagnosis of syphilis and regarded the case as one of osteomyelitis or one of tuberculosis.

Hrdlicka (bibliography, fourth reference) also referred briefly to long bones from Argentina that were probably syphilitic, but of uncertain age.

A skull from Calchaqui, Argentina,[14] was described by von Hansemann (1911). It was thought to be pre-Columbian, but exact data were

14. It was in the Museum für Völkerkunde, Berlin, catalogue no. I C 8877, La Valeta collection, 1906, in the American division of the museum. Prof. Ludwig Pick and Prof. Eugen Fischer endeavored to secure an original photograph of the specimen for me. Apparently von Hansemann had not returned the skull at the time of his death, as it was not in the La Valeta collection; nor could it be found in the museum of the Charité.

wanting; the material from Calchaqui was almost entirely free from European influence.

This skull presented on the forehead a great mass of bony scars, mostly with smooth edges, with flat bulging thickenings of the adjacent areas. Over the orbit on the right was a fresh ulceration of bone. There had been also involvement of the nasal region, with healing. Von Hansemann thought the nasal lesions were more like those of lupus; for the skull as a whole, he made an unqualified diagnosis of syphilis. He gave a fair illustration.

Other reports on skulls from South America alleged to be syphilitic that may be included for the sake of completeness are those of Thulie and Vargara. I have examined their articles, and they seem to me not important.

Bloch gave a quite complete review of the evidence for pre-Columbian syphilis to be had in American bones up to the time that his well known work was published.[14a]

GENERAL SUMMARY

The diagnosis of syphilis from bones can be made to a practical certainty from a perfectly typical syphilitic skull, such as those described in this paper. Undoubtedly, many skulls that are syphilitic are not perfectly typical and would thus be rejected. The diagnosis from long bones is less certain, but in favorable cases a high degree of probability may be attained. In my experience, the inspection of such bones, especially after they have been sawed longitudinally, gives most of the information that can be obtained; but the x-ray picture may give valuable assistance, and the examination of sections with the microscope is sometimes useful. Several other conditions may produce changes more or less resembling those seen in syphilis of long bones. It is possible, though not probable, that some disease producing changes in the bones like those seen in syphilis may have existed in the remote past and have disappeared in recent times.

EASTERN HEMISPHERE

Of a considerable number of alleged finds of ancient syphilitic bones, the following instances are the only ones that I can learn of that are entitled to be called suspicious. It will be observed that they do not concern skulls, but only long bones.

Japan.—A tibia and a fibula described by Adachi and again by Dohi. As far as I can learn, the study of these bones is incomplete, the high antiquity alleged for them is not above suspicion, and no positive diagnosis is warranted.

14a. Three fourths of the references to American material that were known at the time the book was published (1911) are included.

Egypt.—A femur and a tibia alleged to be ancient Nubian, described by Michäelis, who made a diagnosis of probable syphilis, depending on the gross appearance and the examination of sections through the microscope. Nonsyphilitic periostitis could not be entirely excluded; no details are given to prove the antiquity alleged for these bones.

France.—There have been so many alleged finds of syphilitic bones in France that, if they were authentic, the old name, morbus gallicus, would seem justified. After careful analysis, three lots emerge which are suspected of being syphilitic:

1. The tibia from Solutré, which was incompletely studied, and which came from a locality rather notorious for having led to mistakes by archeologists in dating their finds.

2. The humerus and ulna from the valley of the Marne, of the de Baye collection. These were first described by Raymond and have been discussed by many others, and diverse opinions have been offered. Sections were made recently by Michäelis, who diagnosed the condition as syphilis on the strength of the gross and microscopic characters; he stated that his photographs and preparations were submitted to Schmorl, who concurred in the diagnosis. A positive conclusion as to these specimens evidently cannot be reached. De Bayes's collections were made between 1874 and 1888. So long a time has elapsed that it might be well to have the antiquity of these bones checked up by one experienced in modern archeologic technic; in such an important case, the possibility of an intrusive burial should be considered.

3. An ulna and a femur with a probable diagnosis of syphilis and a fragment of a femur with an unqualified diagnosis of syphilis, made by Michäelis on the strength of the gross and microscopic characters. These specimens came from the museum at Saint-Germain. They are called neolithic with no other statement as to their origin.

On the negative side, there is a large amount of evidence from the eastern hemisphere. Practically all recent workers in Egypt reported that they failed to find bones showing evidences of ancient syphilis; Elliot Smith's statement that among more than 25,000 skulls examined by him, not one was syphilitic is impressive. The evidence from France was recently reviewed by Jeanselme and by Pales, both of whom decided that it is inconclusive or negative. In 1896, Virchow stated that he did not know of a single ancient syphilitic bone from any locality; Virchow was probably better informed with regard to osseous material collected in Europe than any other person. I cannot learn of any find in any part of Europe outside of France since the time of Virchow (died in 1902) that can be regarded as highly suggestive of syphilis. Bloch stated that he had searched the Hunterian and other collections

in London and Cambridge, with negative results. The late Professor Boldt of Amsterdam, in a personal conversation, informed me that he had studied many thousands of skulls taken from burial places of various periods; he had never found a syphilitic skull of pre-Columbian date; he had in his immense collection several typical syphilitic skulls of later dates. The late Professor Manouvrier of Paris gave me a practically identical report, also in a personal conversation. In other museums I have had the same experience. It is evident that physical anthropologists who handle vast numbers of ancient bones are keenly interested in the problem of syphilis. It is most unlikely that any authentic specimen of pre-Columbian syphilitic skull has been found in Europe and overlooked. Of course there are enormous territories in Asia and Africa that have never been explored in an archeologic sense.

AMERICA

The six most important finds will be mentioned first:

1. Specimens from Pecos, N. M.: Case 60455, found by Kidder and described by Hooton, is the most convincing. One has the authority of two of the archeologists and anthropologists of the highest standing, acquainted with all that is best in modern technic, for saying that the specimen is pre-Columbian. This skull is syphilitic as far as it is humanly possible to make a diagnosis on a dried skull. The involvement of a femur from the same skeleton is important. Of two other specimens described from Pecos, one is probably syphilitic, and the other possibly so.

2. Second in importance are the skull and long bones from Paracas, Peru, discovered by Tello. The diagnosis of syphilis is as certain as is ever possible in the case of a dried specimen. I examined the ground at Paracas and concluded that only Tello, who was in charge of the excavations, was in a position to form an opinion as to the antiquity of the specimens. Tello is the best known archeologist in Peru and has had a wide experience in archeologic work in various parts of that country. He is of the opinion that the skull is ancient. Although the possibility of intrusive burial is admitted, it is considered most unlikely.

3. The skull from Rio Negro, Argentina, was said by Lehmann-Nitsche to be undoubtedly prehistoric and was pronounced syphilitic by Broca and other French authorities, also by von Hansemann and probably so by Stegmann.

4. Four long bones from a grave in the Cañete Valley, Peru, pronounced prehistoric (proto-Nasca) by a most competent archeologist (A. V. Kroeber), show marked changes due to an osteoperiostitis, probably syphilitic.

5. Fifth are the Mound Builder bones from Ohio. Four lots of long bones pronounced prehistoric by the latest authority on the Mound Builders (Shetrone) have been carefully studied in this paper. All of these show changes consistent with those produced by syphilis; the new growth of bone is evidently periosteal. The results favor a diagnosis of syphilis.

6. Dr. Joseph Jones of New Orleans was the first to claim that evidence of the occurrence of syphilis in ancient bones exists in America. It seems to me that Dr. Joseph Jones is entirely vindicated. Nowhere in his article did he say that the bones were surely pre-Columbian. He did say that some of them were surely syphilitic. One may be confident that Jones knew syphilis of bone when he saw it, practicing, as he did, about 1876 in New Orleans, with its large colored population. His specimens were seen by Klebs in 1896 and pronounced by the latter undoubtedly syphilitic. I was able to locate one skull from this collection. In my opinion it was, in all reasonable probability, a syphilitic skull, though the process on the skull was of moderate severity.

The aforementioned cases have been selected because they are as nearly free from suspicion as any that can be found. It is proper to repeat in this summary the fact that many long bones of Indians showing evidence of disease resembling syphilis have been found in numerous places both in North and in South America. In contrast with the small number of bones from the eastern hemisphere that are suspected of showing ancient syphilis, the amount of material in America is almost embarrassing. In illustration of this fact, I can relate the following experience. In the spring of 1928, Dr. A. Hrdlicka, of the United States National Museum, loaned me thirteen specimens of long bones showing evidence of disease that might be syphilis. They came from Florida, Louisiana, Arkansas and New Mexico, in the United States, and from Pachacamac and Chicama, Peru. Dr. E. C. König, of the Buffalo General Hospital, made roentgenograms of the lot for me, and assured me that if they had been found as modern bones in the ordinary run of practice, at least ten of the thirteen would have been regarded as showing periostitis, probably syphilitic. Dr. Hrdlicka stated that all of these bones were old and that some of them were in all probability pre-Columbian. He was unable to say, however, that any particular bone was pre-Columbian. None of these bones has been described in this report. They represented only a small part of the bones looking like syphilitic bones in the National Museum. I have already stated that the Army Medical Museum has from various southern states about seventy long bones the condition of which was called pre-Columbian syphilis by Moore. Similar material could undoubtedly be found in

many, if not in most, of the large museums. The specimens from Ohio described in this report represent only a portion of those collected by Mills and Shetrone. The early articles of Landon on bones from Ohio, Lamb and Moore on bones from Florida, Joseph Jones and Putnam on bones from Tennessee, Hyde on bones from Colorado and Matthews on bones from Arizona show that such diseased bones, suspected of showing syphilis, have long been known to be numerous and were of widespread occurrence. The total number of such long bones from the United States must have been well into the hundreds. Reports from Peru indicate that such bones were equally common there both on the coast and in the highlands (Eaton, MacCurdy); Argentina has also yielded a considerable number.

The age of these specimens can rarely be determined with certainty, but some of them are surely pre-Columbian. There are few cases of osteitis fibrosa or of Paget's osteitis deformans; the changes in most of them are evidently due to osteoperiostitis, without sinuses or sequestrums. Whitney suggested, years ago, that the Indian's mode of life might have rendered him especially liable to periostitis from wounds. I greatly doubt that the Indians suffered more injury than modern man with his machinery, railroads, automobiles and the like. I have examined many ancient Indian bones, and am of the impression that evidences of fractures are no more frequent, even less frequent, in them than in subjects in the dissecting room today.

Another fact to be noted is that much the larger part of the specimens reported from America come from certain regions only. First there is a great area in the United States beginning in Ohio and extending through the southern states to Florida. Another smaller area seems to have existed in New Mexico and the adjacent states. Another area is in Peru, and another in Argentina; possibly there is one in Mexico and Central America. This may be due in part to these regions being the ones where intensive exploration has been done.[15]

It seems to me that the evidence from bones points clearly to the conclusion that the Indians were afflicted with syphilis in a number of parts of America before the arrival of white men. If this conclusion is correct, one may soon expect to have additional evidence, preferably in the form of skulls undoubtedly syphilitic and undoubtedly pre-

15. When there is more knowledge of the development of immunity in syphilis, that will perhaps throw light on the distribution and spread of syphilis. Certainly, many observers believe that syphilis in the white race was more virulent early in the sixteenth century than it is today, even allowing for improvement in diagnosis and treatment. Recent experimental work also indicates that a certain amount of immunity may be produced in animals under experimental conditions (Chesney).

Columbian.[16] Similar proof from the eastern hemisphere may yet appear, but it has not been produced up to this time.

COMMENT

A few reflections and even speculations on the significance of the facts related in the preceding pages may be permissible. My interest in tracing the origin of syphilis dates from the year 1909, when I prepared a paper that considered infections native to America. In substance, that paper arrived at the conclusion that aboriginal America was singularly free from the great epidemic diseases that are known to have prevailed in the eastern hemisphere.[17] In the twenty-three years that have followed, I have seen no evidence that would modify the main conclusion, although tularemia has been added to the list of infections, and knowledge of tropical leishmaniasis and of several other diseases has been greatly extended. My original conclusion left open for further study the origin of yellow fever and syphilis. The hope that the origin and the antiquity of syphilis might be determined by lesions of the bones seemed not unreasonable. My single excursion into the field of the study of the history of syphilis (1927) led to comments so diverse that one may well despair of finding documentary evidence that will be convincing to everybody.

The origin of the infectious agent of syphilis has been the subject of fantastic speculations from the sixteenth century down to the recent theory of Thugut, not forgetting the llama theory, which had some adherents (Ashmead, 1895). It is therefore with some hesitation that I permit my imagination to take a modest flight.

Proof that men were living in America prior to the last Glacial Period is wanting at present; very likely a few wanderers were here, whose existence would hardly affect the main question. The end of the last Glacial Period may be roughly dated at about 10,000 years ago. Migrants from Asia have crossed Behring Straits at various times since then and have produced the American Indian race. Somewhere and at some time a nonpathogenic spiral organism acquired pathogenic properties and became Spirochaeta pallida. It seems likely that this event

16. Since this paper was written, Dr. Roy L. Moodie has sent me photographs of bones of a Basket Maker from Arizona, around 1800 years old. The skull, one clavicle, one humerus, one femur and one tibia showed the effects of some disease. As far as I can form an opinion from photographs I should think they were syphilitic. Dr. Moodie will give a complete report later on.

17. A parallel exists in the fact pointed out in a recent article by E. D. Merrill (Am. Anthropol., n. s. **33**:379, 1931), who stated that the domesticated plants of the Old and New World were widely spread, each in its own hemisphere, "but none were common to both regions."

took place in America, less than 10,000 years ago.[18] We are accustomed to associate the occurrence of infections with a dense population and large communities, though new infections have not necessarily originated under such conditions exclusively. In America, large settled communities and dense populations became possible when Indian corn, or maize, was developed and cultivated; before that, the Indians were largely wanderers and hunters, subsisting on fish, shell-fish, game, roots, berries and the like. Botanists inform us that Indian corn was probably developed from the grass teosinte (genus Euchlaena), native to the highlands of Mexico and Central America. Its cultivation probably began about 3,000 to 4,000 years ago. Indian corn no longer exists in a wild state. It had been under cultivation long enough for the Indians to have several well marked varieties.

An antiquity for syphilis as slight as even 2,000 years would, I think, present no difficulties to a modern bacteriologist accustomed to the development of rough and smooth, nonvirulent and virulent colonies from one pure culture of bacteria, frequently under conditions that he can easily control.[19] The organism of syphilis has, however, become a parasite of the human body so strict that inoculation of animals produces a disease clinically like syphilis of man only when higher apes are used. It can be cultivated outside of the body with so much difficulty that few strains are under cultivation.

The occurrence of syphilis in pre-Columbian times at points as widely separated as Ohio, New Mexico, Peru and possibly Argentina need present no difficulties. There was plenty of commerce among the Indians. Indian corn was cultivated in all of these areas. Where the seeds of corn could be carried, the seeds of syphilis might also be carried. What now takes place in a few days may then have required centuries, but one is dealing with centuries.

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18. The Indians of tropical America have left behind in their pottery evidence that their minds ran to consideration of sex matters. The large museums often have examples of such pottery, kept behind closed doors, that may be seen on application. The Peruvian Archeological Museum at Lima has an extraordinary collection of this kind of pottery from Peru, some of which represents acts of sexual perversion. This fact may or may not have some bearing on the development of venereal disease.

19. The relationship of syphilis and yaws (frambesia) will ultimately have to be considered in this connection. Some one has said that yaws is "stone-age syphilis." It is also possible that yaws was derived from syphilis. When not only extensive tertiary bone lesions, but also aortic aneurysms are reported in cases of yaws, a pathologist may certainly wonder what he really is dealing with.

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Notes and News

University News, Promotions, Resignations, Appointments, etc.—In the school of medicine of the George Washington University in Washington, D. C., Leland W. Parr has been appointed associate professor of bacteriology; Roscoe R. Spencer, associate professor of hygiene and preventive medicine; John H. Hanks and Elizabeth Verder, assistant professors of bacteriology, and Alden F. Roe, instructor in bacteriology.

Henry E. Sigerist, director of the institute of medical history in the University of Leipzig, has been appointed professor of the history of medicine in the Johns Hopkins University to succeed William H. Welch.

Walter A. Jacobs, chemotherapist, and Karl Landsteiner, pathologist, of the Rockefeller Institute for Medical Research, have been elected members of the National Academy of Sciences.

Society News.—At its recent meeting in Philadelphia the American Society for Experimental Pathology elected Payton Rous president, Carl C. Weller vice-president, and C. Phillips Miller, Jr., secretary-treasurer.

The next meeting of the American Association of Pathologists and Bacteriologists will be held in Washington, D. C., May 2 and 3, 1933, in conjunction with the meetings of the Congress of American Physicians and Surgeons. The president of the association is E. T. Bell; the vice-president, O. T. Avery; the treasurer, F. B. Mallory; the secretary, Howard T. Karsner, and the assistant secretary, Robert A. Moore.

The Italian section of the Societa internazionale di microbiologia will hold its fourth congress next November. Among the subjects to be discussed are microbic dissociation, postvaccinal encephalitis and blood groups in relation to physical constitution.

Recommendations in Regard to Cancer Control in New York State.—The New York State Health Commission recommends in its report as follows:

1. That the state and local departments of health promote the establishment of more adequate facilities for the diagnosis and treatment of cancer, including hospital care and diagnostic tumor clinics with properly qualified physicians in charge and an adequate follow-up service.

2. That qualifications for pathologists in tumor diagnosis and standards for pathological laboratories be prescribed by the Public Health Council, in a manner similar to the systems in effect for public health laboratories.

3. That the State Department of Health continue and extend its efforts to educate the public regarding cancer and that voluntary associations carry out a more aggressive education campaign in this field.

4. That the state division of cancer control effect a working relationship with the committee of the Medical Society of the State of New York which is sponsoring the postgraduate instruction of physicians to develop greater knowledge and increased interest on the part of the profession in the early diagnosis and treatment of cancer.

5. That sufficient appropriations be made to continue and expand the research work now in progress at the State Institute for the Study of Malignant Diseases.

Quarterly Bulletin of the Health Organization of the League of Nations.—The first number is for March, 1932. This periodical will be devoted to work under the auspices of the Health Organization. Forthcoming numbers will contain reports of technical commissions on tuberculosis, venereal diseases, syphilis, medical education, malaria, cancer, etc. The annual subscription is $2.

Abstracts from Current Literature

Experimental Pathology and Pathologic Physiology

METABOLISM STUDIES IN CHRONIC HYPERPARATHYROIDISM IN MAN. J. L. JOHNSON and R. M. WILDER, Am. J. M. Sc. **182**:800, 1931.

The repeated injection of parathormone has produced, in puppies and young rats, a uniform skeletal abnormality that is characteristic of osteoplastic fibrous osteitis (von Recklinghausen). A lacunar resorption of the trabeculae and cortex of bones resulted, with replacement by fibrous connective tissue and osteoid tissue. Giant cells appeared and cysts were formed. The administration of viosterol with parathormone did not modify significantly the end-results. The data of these experiments are reported elsewhere. The present paper deals with observations of the metabolism of a normal human subject who was treated experimentally, first with parathormone, then with parathormone and viosterol. The characteristic disturbances of calcium and phosphorus metabolism produced by injections of parathormone, as well as certain symptoms, notably pain in the bones and weakness of the muscles, characteristic of fibrous osteitis, were not significantly modified by the simultaneous administration of viosterol. The results confirm the view that the genesis of fibrous osteitis, as this disease is observed spontaneously in man, is in an oversupply of parathyroid hormone, and that this disease bears no relation, etiologically, either to osteomalacia or to rickets.

FROM AUTHORS' SUMMARY.

PHYSIOLOGICAL RESPONSES AND IMMUNE REACTIONS TO EXTRACTS OF CERTAIN INTESTINAL PARASITES. H. E. ESSEX, J. MARKOWITZ and F. C. MANN, Am. J. Physiol. **98**:18, 1931.

Studies of the effect on blood pressure of extracts of certain parasitic worms, Taenia pisiformis and Toxascaris canis, showed a marked depressor action, comparable in some respects to the effects of rattlesnake and bee venom, but without the features of swelling of red cells, hemolysis and diffuse hemorrhage. In the case of T. pisiformis, the depressor action was not manifested in dogs heavily infested with the parasite, indicating an apparent ability to develop immunity to the toxic substances.

H. E. EGGERS.

DOES HEMOPHILIC BLOOD CONTAIN AN EXCESS OF AN ANTICOAGULANT? P. S. EVANS, JR., and W. H. HOWELL, Am. J. Physiol. **98**:131, 1931.

Studies of the antiprothrombin content of the blood of a hemophiliac, taken on different days, were made by comparisons with that of three normal persons. No indication whatever was found of excess of the anticoagulant agent, and indeed the results tended to show directly the reverse — less rather than more antiprothrombin. The method of Fuchs for the preparation of the antiprothrombin, with some modifications by the writers, is given with some detail.

H. E. EGGERS.

THE RAPIDITY OF INTERCHANGE BETWEEN BLOOD AND LYMPH IN THE DOG. M. E. FIELD and C. K. DRINKER, Am. J. Physiol. **98**:378, 1931.

After an induced sterile inflammatory process in the dog, the capillaries were found to become abnormally permeable to blood proteins, with the result of a marked increase of the protein content of the subcutaneous lymph. After venous

obstruction there is an outpouring of very dilute subcutaneous lymph in which red cells are usually present. With reduction of blood protein by plasmapheresis, there is associated a marked depletion of the protein content of the subcutaneous lymph and of that of the thoracic duct. The flow of lymph here is greatly increased, and its passage through the capillaries and tissues into the lymphatics must occur with little change in its composition. H. E. EGGERS.

THE EFFECTS OF DENERVATION OF THE LIVER. H. LUNDBERG, J. M. MCDONALD, F. C. HILL and L. V. HILLYARD, Am. J. Physiol. **98**:602, 605 and 610, 1931.

In this series of three related articles, various phases of the effects of denervation of the liver are discussed. This condition was achieved by section of all the structures in the gastrohepatic omentum except the common bile duct, hepatic artery and portal vein. Where there was any doubt as to the section of the branch from the vagus, both vagi were severed in the thorax. With dogs treated in this way, no constant effect was observed on the amount of bile secreted or on the elimination of pigment, on the value of the blood sugar during fasting, on the hyperglycemia produced by epinephrine, dextrose or pituitary extracts, on the hypoglycemia of insulin, nor on the red cell count, the leukocyte count and the coagulation time of the blood. Nor was the action of peptone, in decreasing the number of leukocytes in blood from the liver, affected. H. E. EGGERS.

UREA TOLERANCE AFTER UNILATERAL NEPHRECTOMY IN RABBITS. H. T. KARSNER and ASSOCIATES, J. Exper. Med. **55**:27, 1932.

The method of study has an objective somewhat different from, and lacking the precision of, the ratio of Addis and the urea clearance of Van Slyke. It serves, however, to demonstrate that although for a month after unilateral nephrectomy the remaining kidney shows diminished capacity to hold blood urea within the normal range, nevertheless after four months this function is maintained in essentially the same degree as if both kidneys were present. This does not imply that all activities of the kidney remaining after unilateral nephrectomy are potentially augmented, but the data offered justify the conclusions that as the remaining kidney undergoes enlargement its functional capacity increases, and that the process represents a genuine hypertrophy in the critical sense. AUTHORS' SUMMARY.

PROTECTION OF ADRENALECTOMIZED ANIMALS AGAINST BACTERIAL INTOXICATION BY ADRENAL CORTICAL EXTRACT. F. A. HARTMAN and W. J. M. SCOTT, J. Exper. Med. **55**:63, 1932.

The resistance of adrenalectomized rats to bacterial intoxication has been significantly increased by an extract of the adrenal cortex. This is shown both for acute intoxication with killed Bacillus typhosus and for chronic intoxication with killed Staphylococcus aureus. During the height of the bacterial intoxication, relatively large amounts of the cortical hormone are apparently required to maintain the animals. It is considered probable that a human pyogenic infection imposes a severe load on the adrenal cortex. AUTHORS' SUMMARY.

THE PRODUCTION AND REPAIR OF BONE LESIONS IN EXPERIMENTAL HYPERPARATHYROIDISM. H. L. JAFFE, A. BODANSKY and J. E. BLAIR, J. Exper. Med. **55**:139, 1932.

Young guinea-pigs are more susceptible than adult guinea-pigs to the effects of single or repeated doses of parathormone, as shown by the bone changes. Several successive daily doses of parathormone, in rapidly increasing amount, result in an accentuation of the effects. In young and adult guinea-pigs a com-

pensation is established during prolonged treatment with parathormone, which enables them to tolerate repeated large doses, and which permits considerable repair of bone lesions produced earlier in the treatment.

AUTHORS' SUMMARY.

EXPERIMENTAL NEPHRITIS IN THE FROG. J. OLIVER, J. Exper. Med. **55**:295, 1932.

The apparent similarities in the functional derangements following vascular and parenchymal alterations in the kidney are in fact evidences of a single and identical functional state that may arise from either cause. Functional testing of the kidney cannot, therefore, suffice to determine the condition existing in the kidney. This can be accomplished only by appreciation of the structural alterations present.

AUTHOR'S SUMMARY.

VASODILATATION IN THE LIMBS IN RESPONSE TO WARMING THE BODY, WITH EVIDENCE FOR SYMPATHETIC VASODILATOR NERVES IN MAN. THOMAS LEWIS and GEORGE W. PICKERING, Heart **16**:33, 1931.

A simple method of testing the capacity of arteries of the extremities to dilate is to note the reaction in the cool extremity when the body is exposed to a warm atmosphere. In the hand vasodilatation so induced manifests itself first by a rise of temperature and by brightening in the color of the finger tips. The time at which the response begins is influenced by the initial temperature of the extremities, being delayed by coldness. The response is effected entirely through the sympathetic nerves. By studying the reaction in Raynaud's disease and comparing the effects of ulnar anesthesia, evidence has been obtained that the human sympathetic nerves contain vasodilator as well as vasoconstrictor fibers. The warm chamber is valuable clinically in differentiating obstruction arising from spasm and that arising from structural disease of the arteries. In the former, the response is rapid and proceeds to a high level. In the latter, the response is slow and less pronounced. The chamber can also be used in determining that the sympathetic innervation of vessels of the limb has been lost.

AUTHORS' SUMMARY.

THE IRRESPONSIVENESS AND REFRACTORINESS OF THE VESSELS OF THE SKIN. EDWARD J. WAYNE, Heart **16**:53, 1931.

By electrophoresis it is possible to introduce histamine diffusely into the skin, in low concentration. The vasoconstrictor effect responsible for Bier's spots is capable of overcoming a slight local vasodilatation so produced. It will not prevail over a more intense local vasodilatation caused by histamine. In a similar way Bier's spots appear on areas of local vasodilatation caused by injuries of moderate intensity. They do not invade the intensely reddened areas produced by stroking in a case of factitious urticaria. A Bier's spot may receive electrophoretically, without extinction, a dose of histamine far larger than is necessary to redden control skin. It is concluded that the vessels of the skin under the influence of either histamine or H substance liberated by injury behave similarly toward Bier's spots, when the two are distributed in a comparable way through the tissue spaces. The minute vessels of the skin actively dilated under the influence of small doses of histamine introduced by electrophoresis can be completely constricted by a sufficiently large dose of epinephrine hydrochloride. Larger doses of histamine cause the minute vessels to become completely irresponsive to epinephrine. The minute vessels of the skin actively dilated under the influence of H substance released by injuries of varying degrees of severity behave in a similar way. The local vasodilatation due to slight injury, such as a stroke or a scratch, can be completely obliterated by a large dose of epinephrine hydrochloride. Severe injuries to the skin such as are produced by freezing with carbon dioxide snow give a degree of local vasodilatation that is highly resistant to epinephrine. The

skin inside an area of intense blanching by epinephrine may be injured without causing the vessels to dilate. The minute vessels of skin treated with ultraviolet rays show relative irresponsiveness to epinephrine when tested at various times after irradiation. Relative refractoriness to histamine has been demonstrated similarly. Skin treated with mustard oil exhibits irresponsiveness to epinephrine and refractoriness to histamine. Irresponsiveness of the lesions to epinephrine could be demonstrated in five of six cases of psoriasis examined, varying in degree in different cases. Five cases of psoriasis examined showed refractoriness of the lesions to histamine to a greater or less extent. Refractoriness to the stimulus of a stroke over the site of the psoriatic lesion was demonstrated in a case of psoriasis showing dermatographia. Slight irresponsiveness to epinephrine and considerable refractoriness to histamine were shown in a case of exfoliative dermatitis. It is concluded that all the observations are consistent with the view that the vascular reactions resulting from injury to the skin are due to a liberated substance, either histamine or some substance closely allied to it.

AUTHOR'S SUMMARY.

THE RELATION OF THE LIVER TO THE DISPOSAL OF HEMOGLOBIN. R. MUIR and J. S. YOUNG, J. Path. & Bact. **35**:113, 1932.

When hemoglobin in considerable amounts is introduced into the circulation we fail to find any evidence that it is excreted in the bile. In similar circumstances we also fail to find evidence by microchemical methods that the hemoglobin is taken up by the hepatic cells or by the Kupffer cells. This contrasts with the fact that as a result of hemoglobinemia the renal cells give a distinct iron reaction at a very early stage. The spleen does not show the characteristic swelling that occurs as the result of hemolytic poisons. In chronic hemoglobinemia produced by repeated intraperitoneal injections of hemoglobin solution, an increase of the iron in the liver occurs, but it takes place slowly and does not reach the amount met with in the anemia produced by a hemolytic serum. The reason for this difference is not known. The possibility that in such experiments the iron is carried from local deposits to the liver in some form other than hemoglobin cannot be excluded. In chronic hemoglobinemia, the outstanding feature is the large accumulation of granular hemosiderin in the renal cells, the percentage of iron in them being much higher than in the hepatic cells. The experiments, taken as a whole, have not given support to the view that hemoglobin as such is taken up by the cells of the liver and broken up by them.

AUTHORS' SUMMARY.

RESEARCHES ON BERIBERI. NOEL BERNARD, Ann. Inst. Pasteur **47**:508, 1931.

The etiology of beriberi is exhaustively considered in an article of seventy-two pages. "In résumé, beriberi appears to be a toxic infection, dependent on three essential factors solidly aligned: (1) the toxic organism; (2) a gastro-intestinal medium favoring its action; (3) a state of poor organic resistance resulting from the alimentary régime. If one of these three factors fails, although two others may favor the disease, beriberi will not occur." The author considers extensively the gram-positive sporulating aerobe of the Bacillus megatherium group, B. asthenogenes, which he has been studying for some years.

M. S. MARSHALL.

THE EXCRETION OF SOME DRUGS AND DYES IN THE SPUTUM. J. HERMS, Beitr. z. klin. d. Tuberk. **78**:613, 1931.

The permeability of the bronchial mucosa is similar to that of the salivary glands and that of the gastric mucosa; that is, cations are electively excreted, while anions with the exception of the halogens are not excreted. In inflammation, the alveolar epithelium is permeable for anions and only irregularly for cations.

The permeability can be tested in man most easily with the anion, salicylic acid, and with the cation, antipyrine. The author points out how alterations in the permeability of the respiratory tract can be utilized for diagnostic purposes.

MAX PINNER.

GASTRIC SECRETION IN PULMONARY TUBERCULOSIS. K. MENZEL and M. K. SCHÖFFEL, Beitr. z. klin. d. Tuberk. **78**:654, 1931.

In 100 patients with pulmonary tuberculosis the gastric secretion was studied by the fractionating method. Sixty per cent of the patients showed hyperacidity, 24 per cent normal acidity, 9 per cent hypo-acidity and 7 per cent anacidity. Hyperacidity was particularly frequent in productive disseminating forms and during exacerbations. Only one of the seven patients with anacidity had complete anacidity; that is, this one did not react with acid secretion after histamine, neutral red and insulin had been administered. Symptoms are most marked in patients with hypo-acidity.

MAX PINNER.

ICTERUS DUE TO ARSPHENAMINE. L. STRAUSZ, Dermat. Wchnschr. **93**:1813, 1931.

Rabbits were poisoned with large doses of neoarsphenamine (from 0.6 to 2.4 Gm. per kilogram). The smallest doses caused passive hyperemia of the liver and small interstitial hemorrhages. Later, fat infiltration in the otherwise well stained cells was noted. More severe injury to the parenchyma was evidenced by cloudy swelling and fatty degeneration, and later the nuclei would not stain. The degeneration extended over a large number of cells. Necrotic foci appeared, which were separated from the undamaged cells by a wall of leukocytes. These infarct-like necroses were due to embolic changes in the arterioles. Masses of bile appeared as a result of the damage to the hepatic cells. The degree of damage to the liver closely paralleled the dosage, but widespread hepatic necrosis could not be caused, even with massive doses. The lesions were focal and apparently the result of embolic processes. In the gallbladder, degenerative changes were observed in the epithelium and varied in intensity with the amount of the drug given. Fat droplets appeared in the cells and, resulting from large doses, rather extensive necrosis was seen. Marked fat deposits were found in the fibrous layer of the wall, similar to those seen in the liver; also focal necroses, possibly infarcts. The author concludes that regressive changes occur in the liver and gallbladder in arsphenamine poisoning. The frequent occurrence of necrotic foci resembling infarcts was striking, although definite vascular changes were not found to account for their presence.

LAWRENCE Parsons.

Pathologic Anatomy

DESTRUCTION OF HISTIOCYTES OF THE BLOOD. C. CLASING, Virchows Arch. f. path. Anat. **277**:143, 1930.

White mice were given intravenous injections of india ink or of carmine, and were killed at intervals varying from one-half hour to five months. Immediately following the injection, the endothelial cells of the liver, spleen, lungs, bone marrow, suprarenal glands and intestines took up the injected material. After a time these cells became separated from the tissues in which they lay and entered the blood stream to become the histiocytes of the blood. They were removed from the blood in the capillaries of the liver and spleen, where they were destroyed, in which organs the deposition of large amounts of the injected material takes place. Clasing could find no evidence of destruction of the histiocytes within the lungs.

W. SAPHIR.

EXPERIMENTAL HEMATOPORPHYROSIS OF THE BONES. H. HAMMER, Virchows Arch. f. path. Anat. **277**:159, 1930.

Rats, rabbits, guinea-pigs and one dog were given daily injections of artificial hematoporphyrin for periods varying from a few days to several weeks. As in previous experiments with the natural uroporphyrin, there occurred a typical reddish-brown discoloration of the skeleton and the teeth in growing animals. Adult animals remained unaffected unless an experimental fracture of a bone was produced, in which case the callus and newly formed bone assumed a deep red color as the result of deposition of porphyrin. The porphyrin deposited in the bones and teeth disappeared after a variable period, apparently as the result of its decomposition.

W. SAPHIR.

HISTOLOGIC CHANGES FOLLOWING THE PARENTERAL INTRODUCTION OF AUTOGENOUS PROTEIN. W. JELIN, Virchows Arch. f. path. Anat. **277**:221, 1930.

Twenty guinea-pigs were used in the series of experiments reported here. Two cubic centimeters of blood was withdrawn by cardiac puncture from each animal, and after separation of the serum the latter was injected into the peritoneal cavity of the same animal. The animals were killed at intervals varying from twenty-four to one hundred and five hours. The histologic changes noted were similar to those previously described by the author following the injection of heterologous protein. These changes were: hyperplasia of the reticulo-endothelial system of the liver, spleen and lymph nodes; dilatation of the capillaries and larger vessels of all the internal organs, with inflammatory reaction of the walls of the vessel; disturbance of the carbohydrate metabolism of the liver, characterized by marked glycogen infiltration of the liver and hyperglycemia; a slowly developing glomerulonephritis, with congestion, minute hemorrhages and cellular infiltration of the glomeruli and degeneration of the tubular epithelium; enlargement, hyperplasia and increased pigment formation in the suprarenal glands.

W. SAPHIR.

THROMBOSIS OF THE INFERIOR VENA CAVA IN A NEW-BORN INFANT. W. EILERS, Virchows Arch. f. path. Anat. **277**:248, 1930.

Thrombosis of the inferior vena cava occurred in an infant 15 days old. The thrombosis was followed by hemorrhagic infarction of both kidneys and both suprarenal glands. Thrombosis was also noted in the dural sinuses. Since inflammation was present in the region of the umbilicus, the thrombosis is considered to have been infectious in origin.

W. SAPHIR.

PERIRENAL HEMORRHAGE. P. HEILMANN, Virchows Arch. f. path. Anat. **277**: 256, 1930.

Four cases are described in which large perirenal hematomas were found. In two, the condition was discovered in the course of a surgical operation, and in two, at necropsy. Of the latter, one was a case of scarlet fever; the other, a case of nephrosclerosis with cerebral hemorrhage. The hemorrhage was unilateral in each case, and no apparent cause for it could be found. The possibility of reflex nervous action is discussed. Histologic examination revealed necrosis of the capillary endothelium and pericapillary leukocytic infiltration.

W. SAPHIR.

CHANGES IN THE HEAD OF THE FEMUR FOLLOWING FRACTURE OF THE NECK. E. Freund, Virchows Arch. f. path. Anat. **277**:326, 1930.

The changes that occur in the head of the femur following fracture of the neck of the femur depend on the degree to which the blood supply of the head is involved. If the blood supply is completely abolished, the bone and the marrow become necrotic and may undergo partial resorption. The cartilage of the head is

usually preserved, because it obtains adequate nutrition from the synovial fluid. The extent to which the blood supply of the head is interfered with by fracture of the neck depends on the degree of injury to the round ligament. If the blood vessels of the ligament remain intact, partial necrosis of the head may be followed by new formation of bone and restitution of the head.

W. SAPHIR.

DIVERTICULUM OF THE HEART. S. MAHRBURG, Virchows Arch. f. path. Anat. **277**:498, 1930.

The unusual anomaly was found at necropsy in a boy 3 days old. Extending from the apex of the left ventricle to within 1 cm. of the umbilicus was a funnel-shaped diverticulum in which the lumen was continuous with the cavity of the ventricle. Associated maldevelopments were: defective ventricular septum, hare-lip, cleft palate, acrania and fusion of the dura with the fetal membranes. The probable explanation of the cardiac anomaly offered is fusion of the region of the cardiac apex with the fetal membranes early in development, leading to traction and the formation of the diverticulum.

W. SAPHIR.

MYXOFIBROMA OF THE ENDOCARDIUM. M. D. ARIOL, Virchows Arch. f. path. Anat. **277**:501, 1930.

The report relates to a new-born infant who had manifested the clinical symptoms of cardiac failure during the two days that it lived. At necropsy there were found, on both the mitral and the tricuspid valves, tumor-like papillary outgrowths that extended into the cavity of the ventricles. Histologic examination revealed no evidence of fetal endocarditis. The outgrowths were the result of proliferation of the subendothelial stroma. They were developmental in origin, the process being one of localized excess formation of tissue.

W. SAPHIR.

OBLITERATION OF THE PERIPHERAL BRANCHES OF THE PULMONARY ARTERY. A. GOEDEL, Virchows Arch. f. path. Anat. **277**:507, 1930.

In two cases of hypertrophy and dilatation of the right side of the heart, there was obliteration of terminal branches of the pulmonary artery, the result probably of thrombosis or of embolism, with subsequent organization and recanalization. Arteriosclerosis, syphilis and nonspecific inflammation must also be taken into account in such obstruction of the pulmonary circulation. Obstructive lesions of the smaller pulmonary arteries may be the explanation of those cases of hypertrophy and dilatation of the right side of the heart in which one often finds only slight chronic bronchiolitis or slight moderate emphysema.

W. SAPHIR.

THE ACTION OF INTRAVENOUSLY INTRODUCED COLLOIDAL SILVER. H. KOLLER-AEBY and T. KOLLER, Virchows Arch. f. path. Anat. **278**:84, 1930.

The therapeutic intravenous administration of colloidal silver in infection has been employed since the procedure was proposed by Credé in 1895. Although the distribution of the deposited silver in experimental normal animals has been studied, there is little precise knowledge of the distribution of the silver and its probable mode of action in inflamed human tissues. This report is based on the histologic study of tissues removed in six fatal cases of infection, in which colloidal silver had been used, and of an acutely inflamed appendix from a patient who had received two intravenous injections of colloidal silver previous to appendectomy. In confirmation of the observations of others made on animals, deposition of silver in granular form was noted in the reticulo-endothelial system and especially in the Kupffer cells of the liver. The deposition of granular silver compounds was most marked in the inflamed tissues, and the intensity of the deposition

ran parallel with the severity of the local inflammatory process. The deposition is ascribed to local acidosis of the inflamed tissues, the silver being precipitated as inorganic salts. It is to the latter that colloidal silver owes such therapeutic action as it may have.

O. T. SCHULTZ.

SYPHILITIC ULCER OF THE STOMACH. G. L. DERMAN and M. A. KOPELOWITSCH, Virchows Arch. f. path. Anat. **278**:149, 1930.

For the clinician, syphilis of the stomach is not a rare disease. For the pathologist, it is extremely rare. The authors report an ulcerative lesion of the stomach that they believe to be syphilitic, and not merely a coincidental peptic ulcer in a person with syphilis. The patient, aged 31, died of lobar pneumonia following an acute hemorrhage of the stomach. Autopsy revealed, in addition to the pneumonia, syphilitic cirrhosis of the liver with multiple gummas and amyloid infiltration of the spleen and kidneys. In the prepyloric region of the stomach there was a saddle-shaped ulcer of the greater curvature. The floor of the ulcer, which was covered at the margins by a thin layer of mucosa, was formed by a greatly thickened submucosa with perivascular lymphocytic infiltration and obliterating endarteritis of the larger arteries. The granulomatous process extended down into the muscle coats.

O. T. SCHULTZ.

DERMOID OF THE CEREBELLUM. M. KORNFELD, Virchows Arch. f. path. Anat. **278**:165, 1930.

The lesion described occurred in a woman, aged 33, who had suffered with headache since the age of 15 and with symptoms of increased intracranial pressure for two months previous to death. The tumor was the size of an almond and was situated in the pia of the inferior anterior surface of the vermis of the cerebellum. It had caused dilatation of the ventricular system. It contained small areas of bone, cholesterol crystals, hair follicles and hairs. Some of the latter had penetrated the cerebellum and had led to minute herniations of cerebellar tissue along the hairs. The tissue was the seat of inflammatory reaction, characterized by lymphocytic and plasma cell infiltration and by fibrosis. The lesion is ascribed to embryonic misplacement of epidermis. The author tabulates thirty-two examples of intracranial dermoid recorded from 1745 to 1927. He tabulates also twenty-one previously reported cases of epidermoid, dermoid and teratoid tumors of the cerebellum. Seven of these were dermoids.

O. T. SCHULTZ.

CONGENITAL ATRESIA OF THE DUODENUM WITH DUPLICATION OF BILE AND PANCREATIC DUCTS, K. KATZ, Virchows Arch. f. path. Anat. **278**:290, 1930.

Atresia of the duodenum in a child that died on the seventh day after birth was associated with duplication of the distal portion of the ductus choledochus and of the pancreatic duct. One bile duct and a pancreatic duct entered the duodenum above the atresia; the other pair, below the atresia.

O. T. SCHULTZ.

CONGENITAL ATRESIA OF THE TRANSVERSE COLON. H. POPPER, Virchows Arch. f. path. Anat. **278**:295, 1930.

Congenital stenosis and atresia of the intestinal tract occur most frequently in the anus and rectum and next most frequently in the duodenum. The condition is seen less often in the jejunum and lower end of the ileum and least frequently in the colon. In the case presented, that of a stillborn, full-term infant, the ascending colon was greatly enlarged and ended blindly. It was not normally attached to the lateral body wall, and the blind end lay in the left iliac fossa. The transverse colon was represented by a narrow cord 8 cm. long in the border of the transverse mesocolon. Microscopic examination revealed no intestinal tissue in this cord. The blind end of the distal colon was situated at the lower pole of the spleen and

corresponded to the splenic flexure. The rectum was also atretic. In his discussion of the mechanism of the conditions found, the author devotes chief attention to the enlargement of the blind ascending colon. The enlargement was not due entirely to simple mechanical distention, but in part at least to marked hypertrophy of the wall. The author believes that the anomaly described was the result of two simultaneous errors of development. One was hypertrophy and overgrowth of the ascending colon, similar to the process that leads to congenital megacolon of Hirschsprung. The other was an inhibition of development that led to atresia of the transverse colon and rectum.

O. T. SCHULTZ.

CONSTITUTIONAL VARIATIONS IN CRANIAL FORM AND OXYCEPHALY. H. GÜNTHER, Virchows Arch. f. path. Anat. **278**:309, 1930.

Günther presents measurements of a number of variations in cranial form that he believes to be dependent on constitutional factors, and discusses the variations in relation to oxycephaly, for which he prefers the name akrocranium. Oxycephaly, which is due to hypoplasia or retarded development of the base of the skull, is often merely a subjective impression. Substantiation of this impression requires deviation from normal cranial measurements and indexes of a definite order of magnitude. Most important are the measurements and indexes that express the relationship of cranial circumference to height. Two pure types of akrocranium are recognized, one with, the other without, exophthalmos and angular deformity of the maxilla. The cranial deformity is often associated with impairment of vision (akrocraniodysopia), increased fragility of the erythrocytes and hemolytic icterus (akrocraniodyshemia) and phalangeal abnormalities (akrocraniodysphalangia). Although the cranial deformity may be due to mechanical factors acting on the fetus after development has been initiated, in which case the deformity is an acquired one, in the majority of instances the deformity is the result of abnormalities in the genetic constitution of the germ plasm. The associated abnormalities Günther also believes to be constitutional in nature.

O. T. SCHULTZ.

THE EARLIEST TISSUE CHANGES IN ACUTE RHEUMATIC INFECTION. F. KLINGE, Virchows Arch. f. path. Anat. **278**:438, 1930.

Klinge describes, as the earliest tissue change in acute rheumatic fever, serous infiltration of the ground substance of connective tissue. This proceeds rapidly to fibrinoid degeneration and disorganization of the tissue. These changes have been noted in the capsule of the tonsil, the liver and the spleen, in the walls of blood vessels, in the synovial membranes and joint capsule, and in the connective tissue of the myocardium and of voluntary muscle. The exudative-degenerative reaction is followed by cellular infiltration of variable degree by lymphocytes and leukocytes. Cellular infiltration soon becomes associated with proliferation of the fixed tissues. The exudative-degenerative reaction and the cellular infiltrative-proliferative reaction are not two different types of reaction in acute rheumatic fever, but are successive stages of the changes that occur in the tissues. The exudative-degenerative reaction is the result of local tissue allergy.

O. T. SCHULTZ.

CONGENITAL MALDEVELOPMENTS: ATRESIA OF THE SMALL INTESTINE. G. BODON, Virchows Arch. f. path. Anat. **278**:529, 1930. VENTRAL HERNIA. Z. SZANTROCH, ibid., p. 539. MALDEVELOPMENTS OF THE CEREBELLUM. H. TESSERAUX, ibid., p. 555. COMPLETE AND UNILATERAL ABSENCE OF VERTEBRAL BODIES. A. FELLER and H. STERNBERG, ibid., p. 566.

Four successive contributions are devoted to examples of congenital maldevelopments of the types indicated by the titles. Each reviews the theories that have been propounded in explanation of the genesis of the particular anomaly and attempts to interpret the latter in the light of these theories.

O. T. SCHULTZ.

SILICOSIS OF THE LUNG. H. BERGSTRAND, Virchows Arch. f. path. Anat. **278**:647, 1930.

The older literature on pneumonoconiosis ascribed the fibrosis of this condition to the mechanical action of the inhaled particles. More recent studies of pulmonary silicosis ascribe a greater rôle to the physicochemical action of colloidal silicon than to the particulate character of the material. The greater degree of change caused in the lung by some silicious materials as compared with others may be due to the chemical composition. Since coal dust, stone dust and other inspired materials contain appreciable quantities of silicon, it is probable that the action of colloidal silicon is the primary factor in the various pneumonoconioses. Bergstrand describes briefly the histologic changes in silicosis and correlates these with the roentgenologic changes in the first, second and third stages of the disease. The first stage is characterized by localized thickening of the alveolar septums, degeneration of elastic fibrils, localized emphysema and collagenous thickening of the interlobular septums. In the second stage, the lymphoid follicles of the lung are transformed into tubercle-like fibrotic nodules. In the third stage, there occur serous and fibrinous exudation into the alveoli, collapse of central portions of the lung and organization of the collapsed areas by fibrous tissue. The three stages represent merely quantitative differences in degree of the same process, not qualitatively different forms of tissue reaction.

O. T. SCHULTZ.

TUBEROUS SCLEROSIS. H. FERIZ, Virchows Arch. f. path. Anat. **278**:690, 1930.

Feriz devotes eighty pages to a detailed and richly illustrated description of a case of tuberous sclerosis that presented many interesting features. Chief among these was the fact that the patient, a woman, reached the age of 25 years, was psychically normal, and had never had any epileptiform seizures. Second in importance was the rare anomaly, crossed dystopia of the kidney. Removal of the fused single kidney, under the preoperative diagnosis of sarcoma of the left kidney, was followed by anuria and death. The malformed kidney was the site of a mixed tumor that contained areas of differentiated muscle, fat and angioma, areas of undifferentiated myosarcoma, liposarcoma and angiosarcoma, and still other areas in which the sarcoma tissue appeared to be undergoing transformation into carcinoma. The left vertebral artery arose from the arch of the aorta. Each retina contained several minute nodules that histologically were found to be gliomatous. There were a number of similar subependymal nodules. The tuberous areas of the brain contained no ganglion cells. Some consisted of differentiated excessive glia, still others of cellular gliomatous tissue, and in some the cellular tissue appeared to be undergoing transformation from sarcoma-like tissue to tissue of epithelial character. The patient had adenoma sebaceum of the face, a condition not infrequently associated with tuberous sclerosis. Feriz looks on tuberous sclerosis as primarily a congenital maldevelopment characterized by inhibition of development and of differentiation of the tissues of more than one organ system. The tissue, the development of which has been inhibited, may at some later period undergo blastomatous transformation.

O. T. SCHULTZ.

Microbiology and Parasitology

COCCIDIOIDAL GRANULOMA. California Dept. Pub. Health, Special Bulletin 57, 1931.

This bulletin reviews the knowledge of coccidioidal granuloma as it occurs in California. A complete bibliography on coccidioidal granuloma is included. The early history of the disease in California is reviewed by Emmet Rixford, a pioneer worker on the disease. The etiology and symptomatology are discussed by Ernest C. Dickson; the diagnostic laboratory procedure and epidemiology, by N. Dorthy Beck.

THE RESISTANCE OF DEHYDRATED PNEUMOCOCCI TO CHEMICALS AND HEAT. F. P. GAY, K. N. ATKINS and M. HOLDEN, J. Bact. **22**:295, 1931.

Pneumococcus type I in the form of both virulent and avirulent ("smooth" and "rough") dissociants is susceptible when grown in broth to the usual disinfectants, heavy metals, dyestuffs, anhydrous solvents, phenol and iodine, and to certain more or less specific substances such as ethylhydrocupreine hydrochloride and bile salts. In two instances it could be shown (mercuric chloride, ethylhydrocupreine hydrochloride) that the "smooth" organism was more readily killed than the "rough" form. When the micro-organisms are collected by centrifugation and rapidly dried to constant weight over calcium chloride, a large proportion of the cells are killed, the surviving percentage depending on the technic employed. The surviving pneumococci may continue to decrease in number, but some, at all events, survive for as yet undetermined periods — for eighteen months at least. Desiccated but living pneumococci of both forms "R" and "S" are not killed in the absence of water by alcoholic solutions of the substances described, except in the case of the heavy metals (mercury salts, silver nitrate). Dried "S" pneumococci, contrary to the findings in moist cultures, are more resistant to mercuric chloride than the "R" forms. The thermal death point of moist "R" pneumococci (56 C.) is distinctly higher than that of moist "S" pneumococci. When the two dissociants are dried they both resist heating to 115 C. for thirty minutes, but are killed by exposure to temperatures of 120 C. and above.

AUTHORS' SUMMARY.

THE BEHAVIOR OF RICKETTSIA PROWAZEKI IN TISSUE CULTURES. H. PINKERTON and G. M. HASS, J. Exper. Med. **54**:307, 1931.

Typhus Rickettsiae are found in large numbers in sections of tissue cultures of scrotal sac exudate. Extensive multiplication of the organisms occurs, and new cells become infected. Organisms are seen in cells undergoing mitotic division. The organisms usually become less numerous after the sixth day in vitro, but in one instance organisms were extremely numerous on the sixteenth and twenty-first days. Rickettsiae in tissue cultures retain their intracellular location, even when infection is very heavy. They multiply exclusively in nonphagocytic cells, which are believed to be of mesothelial origin. Pleomorphism is much more pronounced in tissue cultures than in guinea-pig tissues, and is entirely comparable to that seen in the louse.

AUTHORS' SUMMARY.

TOXIC PROPERTIES OF FILTRATES OF HEMOLYTIC STAPHYLOCOCCUS AUREUS. J. T. PARKER WELD and A. GUNTHER, J. Exper. Med. **54**:315, 1931.

Sterile filtrates from certain hemotoxic strains of Staphylococcus aureus have several toxic properties, of which the most important are the hemotoxic, the necrotoxic, the leukocidic and the property of killing rapidly. The necrotoxic action appears to be caused by a constituent in the filtrates different from either the hemotoxic or the leukocidic one.

AUTHORS' SUMMARY.

SWINE INFLUENZA: EXPERIMENTAL TRANSMISSION AND PATHOLOGIC ANATOMY. R. E. SHOPE, J. Exper. Med. **54**:349, 1931.

Swine influenza has been induced in pigs by the intranasal instillation of material from spontaneous cases of the disease occurring epizootically in eastern Iowa. The experimental disease has the same features as the epizootic. It has been maintained for study by serial passages accomplished either by intranasal instillation or by pen contact. Eight strains of the virus have been established experimentally during three epizootic periods. The clinical disease induced by these eight strains has been, in general, the same, although its severity and mortality have varied. The principal features of the pathology of swine influenza are an

exudative bronchitis accompanied by marked damage of the bronchial epithelium and its cilia, a peribronchial round cell infiltration and massive pulmonary atelectasis. The latter is modified somewhat by a round cell infiltration of the alveolar walls. The lymph nodes, especially the cervical and mediastinal ones, are hyperplastic and edematous. There is usually a mild to moderate, acute splenic tumor. The mucosa of the stomach and colon is congested. The pneumonia following swine influenza is, characteristically, lobular in type and of the same general distribution as the atelectasis. The nonpneumonic areas of lung are extremely edematous and congested.

HEMOPHILIC BACILLUS FROM RESPIRATORY TRACT IN SWINE INFLUENZA. P. A. LEWIS and R. E. SHOPE, J. Exper. Med. **54**:361, 1931.

A hemophilic bacillus has been regularly obtained in culture from the respiratory tract of a series of swine experimentally infected with swine influenza and from a small number of spontaneous field cases of the disease. It has not been observed in respiratory tract cultures from a group of swine free from influenza. The cultural and morphologic characters of the organism have been described, and the name Hemophilus influenzae (variety suis) suggested. The organism exhibits marked serologic diversity, since only two of eight strains studied were serologically identical. It is usually nonpathogenic for rabbits and white rats, and irregularly pathogenic for white mice. One strain of the organism was pathogenic for guinea-pigs, while two others were not. Eleven of thirteen attempts to induce symptoms of disease in swine by intranasal inoculation with pure cultures of H. influenzae-suis were entirely negative. The remaining two attempts, which suggested a positive result, have been discussed. Attention has been called to the marked similarity that exists between nonindol-producing strains of H. influenzae-suis.

FILTRATION EXPERIMENTS AND ETIOLOGY IN SWINE INFLUENZA. R. E. SHOPE, J. Exper. Med. **54**:373, 1931.

It has been possible to demonstrate, in Berkefeld filtrates of infectious material from experimental cases of swine influenza, a virus that when administered intranasally to susceptible swine induced a mild, usually afebrile illness of short duration. The changes in the respiratory tract resembled those in swine influenza, but were usually much less extensive. When the filtrable virus was mixed with pure cultures of H. influenzae-suis and administered to swine a disease identical clinically and pathologically with swine influenza was induced. The data presented indicate that the filtrable viruses of swine influenza and H. influenzae-suis act in concert to produce swine influenza and that neither alone is capable of inducing the disease. One attack of swine influenza usually renders an animal immune to reinfection. Blood serum from an animal made immune in this way neutralizes infectious material from swine influenza in vitro, as shown by the failure of the mixture to produce disease in a susceptible animal. The virus can be stored in a dried state or in glycerol for several weeks at least. In one instance, dried material apparently retained both the virus and H. influenzae-suis in viable form for a period of fifty-four days. Fatal cases of experimental swine influenza have been observed in which H. influenzae-suis was the only organism that could be cultivated from the respiratory tract. Attention has been called to some features of marked similarity between epizootic swine influenza and epidemic influenza in man.

AUTHORS' SUMMARIES.

PROTEIN FRACTIONS OF A SCARLATINAL STRAIN OF STREPTOCOCCUS HEMOLYTICUS. M. HEIDELBERGER and F. E. KENDALL, J. Exper. Med. **54**:515, 1931.

A tentative method is described for extracting a labile nucleoprotein from scarlatinal Streptococcus hemolyticus. The product differs chemically and sero-

logically from the fractions prepared by subsequent alkaline extraction of the cell residues, and from protein obtained by the classic method for the extraction of bacterial "nucleoproteins." The new nucleoprotein is sensitive to weak alkalis and readily loses nucleic acid under these conditions. The protein degradation products resemble the alkaline-extracted protein fractions of the cell residues. The bearing of the properties of the new nucleoprotein on the chemistry of nucleoproteins in general is discussed, also the possible relation of the fractions obtained to the analysis of streptococcus antigens made by Lancefield.

AUTHORS' SUMMARY.

THE TRANSMISSION OF THE VIRUS OF MEXICAN TYPHUS FROM RAT TO RAT BY POLYPLAX SPINULOSUS. H. MOOSER, M. R. CASTANEDA and H. ZINSSER, J. Exper. Med. **54**:567, 1931.

Polyplax spinulosus, the common rat louse, is easily infected with the virus of typhus by feeding on infected rats. As in the case of Pediculus humanus, such feedings are followed by the appearance of large numbers of Rickettsia prowazeki within the intestine of the insect. The virus of Mexican typhus can be transmitted from rat to rat by Polyplax spinulosus by methods of feeding simulating natural conditions. It seems, therefore, that this ectoparasite is an important factor in maintaining an endozoic of Mexican typhus among wild rats.

AUTHORS' SUMMARY.

THE RELATIONSHIP OF CERTAIN VARIANTS OF B. TYPHOSUS. F. B. GRINNELL, J. Exper. Med. **54**:577, 1931.

The results of cross-agglutination and agglutinin absorption experiments with the motile smooth, nonmotile smooth, motile rough and nonmotile rough forms of B. typhosus are presented. Cross-agglutination between these four forms is complete, save that the motile rough antigen is under certain conditions only weakly agglutinated by the antiserums prepared with the nonmotile forms. Cross-absorption of the somatic agglutinogen of the four variants is complete, save that the motile smooth culture still shows granular agglutination with the anti-MS and anti-MR serums after absorption with these cultures. A theory of the antigenic composition of the four variants of B. typhosus is presented, based on the results obtained in these experiments. It would appear that, contrary to the usually accepted theory, the four variants have a common somatic agglutinogen. To explain the difference between the smooth virulent forms and the rough nonvirulent forms it has been assumed that the S forms contain a carbohydrate that is associated with virulence and which takes no part in the agglutination reaction.

AUTHOR'S SUMMARY.

AN ALBINO RAT COLONY FREE FROM MIDDLE EAR DISEASES. J. B. NELSON and J. W. GOWEN, J. Exper. Med. **54**:629, 1931.

A special colony of albino rats was built up by selection and isolation from a population in which middle ear disease was highly prevalent. No cases of aural infection occurred in the selected group, whereas its precursor showed a crude incidence of 57 per cent. The subjection of selected rats to a rachitic diet and to overcrowding did not predispose to the development of middle ear disease. The incidence of pneumonia was not similarly affected; thus, 52 per cent of the adult selected rats and 78 per cent of the adult stock rats showed pulmonary lesions. There was, however, a significant reduction in the number of cases that showed advanced pulmonary lesions. Certain theoretical considerations of middle ear disease and of pneumonia are discussed.

AUTHORS' SUMMARY.

ARTIFICIAL ACIDOSIS IN TRYPANOSOMA LEWISI INFECTIONS. R. W. LINTON and H. A. POINDEXTER, J. Exper. Med. **54**:669, 1931.

When the alkali reserve is artificially lowered in rats infected with Trypanosoma lewisi, the number of parasites in the blood is increased. The increase is large in the early stages of the disease, and becomes less marked as the number crisis is approached. Near the crisis, and after it, a lowered alkali reserve does not affect the number of trypanosomes. It has been shown that the observed increase does not result from a contraction of the capillaries of the inner organs, which would throw a large number of trypanosomes into the peripheral circulation, nor is the increase due to a greater reproductive activity on the part of the trypanosomes. The increase must, therefore, be due to an inhibition of the destructive forces of the host. It is suggested that the known production of organic acids by the pathogenic trypanosomes plays a similar rôle in inhibiting the destructive mechanism of the host, and is therefore of significance in the pathogenic activity of these organisms.

AUTHORS' SUMMARY.

IN VITRO TRANSFORMATION OF PNEUMOCOCCAL TYPES. M. H. DAWSON and R. H. P. SIA, J. Exper. Med. **54**:681 and 701, 1931.

Type-specific S pneumococci may be transformed from one specific S type into other specific S types entirely by in vitro methods. R forms of pneumococci, derived from S forms of one specific type, may be transformed into S forms of other specific types by the following in vitro procedure: the growth of small inocula of R forms in mediums containing vaccines prepared from heterologous S cultures. Transformation of type may be effected in this procedure by the use of small quantities of S vaccine, quantities representing the bacteria from as little as 0.1 cc. of the original culture. Transformation of type, as induced by this procedure, is most readily effected by employing anti-R serum in the culture medium. Transformation of type may be effected, however, in mediums that do not contain anti-R antibodies. Previous findings on the thermal characteristics of the property of S vaccines responsible for transformation of type have been confirmed and extended.

Further observations on the conditions under which transformation of pneumococcal types may be induced by in vitro procedures are presented. R cultures possessing only slight degrees of R stability are most suitable for transformation purposes by in vitro procedures. Vaccines prepared from cultures subjected to the action of bacterial enzymes liberated in old broth cultures, and during mechanical disruption of young bacterial cells, are not effective in inducing transformation of type. The property of an S vaccine responsible for transformation of type is not related to the specific soluble substance of pneumococcus. Attempts to effect transformation of type by the use of cell-free extracts of pneumococcus have so far proved unsuccessful.

AUTHORS' SUMMARIES.

CERTAIN MONILIAS PARASITIC ON MAN. R. W. BENHAM, J. Infect. Dis. **49**:183, 1931.

The parasite found in thrush, here referred to as Monilia albicans, is a well defined species which can be recognized and differentiated from related forms by its morphologic and cultural characteristics. M. psilosis of Ashford is apparently identical with M. albicans isolated from thrush. Many of the yeastlike organisms found in erosio interdigitalis, in chronic paronychias, in perlèche, in other dermatoses and in certain types of superficial glossitis should for the present be placed in this same species. Other species showing slight, but definite, morphologic differences are found on the skin and in sputum and feces. Thirty strains of Monilia were tested for virulence. Nineteen, identified as M. albicans, from various sources, were pathogenic for rabbits. Eleven strains of other types produced no lesions. Seven strains of M. albicans proved similar in antigenic content

as determined by the reciprocal absorption of agglutinins. The slight differences detected could not be correlated with the sources from which these strains were obtained. Agglutinative reactions, when used in conjunction with other methods, were found the most satisfactory means for the identification of these rudimentary forms.

AUTHOR'S SUMMARY.

THE INFLUENCE OF PUS AND BLOOD ON THE ACTION OF BACTERIOPHAGE. M. APPLEBAUM and W. J. MACNEAL, J. Infect. Dis. **49**:225, 1931.

Purulent exudate exerts a marked inhibitory influence on the lytic action of the antistaphylococcus bacteriophage, sufficient to explain the persistent survival of the bacteria in purulent collections within the body of a patient receiving treatment with potent bacteriophage. Even when diluted 1:1,000, a purulent exudate sometimes exerts a relative inhibitory effect in vitro. Heating the pus at 60 C. for thirty minutes diminishes this inhibitory effect only slightly. Similar dilutions of purulent exudate failed to show an analogous inhibitory influence on the lytic action of anticolon-bacillus bacteriophage. Undiluted citrated blood, undiluted defibrinated blood and diluted blood serum exercise an inhibitory influence on the antistaphylococcus bacteriophage, but there is considerable variation in behavior of different bacterial strains and apparently in behavior of different races of bacteriophage. Undiluted blood did not permit the multiplication of the colon bacillus under the experimental conditions employed, and the experiments with diluted serum failed to reveal a clearly evident inhibition of the anticolon-bacillus bacteriophage.

AUTHORS' SUMMARY.

INFECTION OF THE ACCESSORY SINUSES AND UPPER RESPIRATORY TRACT IN AVITAMINOSIS OF RATS. R. G. TURNER and E. R. LOEW, J. Infect. Dis. **49**:244, 1931.

The bacterial flora of the nasal cavities and middle ears of ninety-two albino rats is reported. A comparison is made of the bacteria encountered in these localities when they present suppurative lesions with the flora when suppuration is absent. Staphylococcus aureus, chromogen 6 and the colon bacillus were the outstanding pyogenic organisms encountered in the suppurative lesions. The incidence of chromogen 6 was greater in the suppurative, than in the nonsuppurative, loci in the xerophthalmic animals. The variations in the percentage of the staphylococci were relatively slight, while colon bacilli were encountered most abundantly. Environmental conditions apparently played a part in the incidence of colon bacilli and of staphylococci. The age of the animal, the previous storage of vitamin and the season had no marked effect on the bacterial flora. Environmental conditions were not responsible for the increased incidence of chromogen 6. Comparison of the three series investigated showed that this organism gained in percentage incidence with increased severity of the disease produced by the withdrawal of vitamin A. Experimental evidence is given to substantiate the alterability of this organism toward the Gram stain. Provisionally it remains to be classified as a chromogenic, gram-negative coccus falling in group 6 of Gordon's classification. Chromogen 6 apparently has an elective affinity for the mucous membrane of the upper respiratory tract and nasal cavities. It fails to thrive when injected intraperitoneally or intramuscularly into common laboratory animals. The pathogenicity of chromogen 6 is attributed largely to the lowered resistance of the mucous lining of the nasal cavities, brought about primarily through withdrawal of vitamin A from the diet.

AUTHORS' SUMMARY.

EFFECT OF BACTERIOPHAGE ON ANTHRAX IN WHITE MICE. P. B. COWLES and W. M. HALE, J. Infect. Dis. **49**:264, 1931.

These experiments are based on a special case — the use of bacteriophage in anthrax in white mice — but the nature of the factors present would seem to be

exceptionally well suited for definite results. The mouse is so highly susceptible to the disease that most of the controls succumbed to the almost surely fatal dose used. The strain of anthrax used was quickly and permanently lysed by the bacteriophage in high dilution. That no protection resulted from the administration of bacteriophage in several ways and that even contact between organisms and bacteriophage before injection usually failed to inactivate all of the former seem most significant in the present case, and may suggest the reasons for failure of bacteriophage therapy in other diseases. Under such experimental conditions bacteriophage simply does not seem able to act efficiently, if at all, in the tissues. That it was present and could be recovered even after death is all the more striking, although whether the principle recovered was some of the original material injected or whether it had developed very slowly in the body cannot be stated. It may be added that tentative experiments designed to show whether bacteriophage used as an antigen has any immunizing value against anthrax in mice, guinea-pigs and rabbits failed to demonstrate any protection. However, such variable factors as the amount of bacteriophage injected, the frequency of the injections and the time requisite for the development of immunity were not studied exhaustively, so that no final conclusion can be drawn.

AUTHORS' SUMMARY.

ELECTROPHORETIC STUDY OF STREPTOCOCCI OF SCARLET FEVER AND ERYSIPELAS. L. E. SHINN, J. Infect. Dis. **49**:281, 1931.

The growth of the organisms of scarlet fever and erysipelas in a standard medium produce similar, but distinctly different, changes in the electronitrogen picture. The changes in buffering action produced by the growth of these organisms are different and show a relationship to the changes in the values of the migratory nitrogen. The toxin of scarlet fever alters its charge sharply between p_H 7.03 and p_H 7.38. It does not exist in the filtrates as a simple free substance.

AUTHOR'S CONCLUSIONS.

ERGOSTEROL CONTENT OF MYCOBACTERIUM. P. S. PRICKETT and O. N. MASSENGALE, J. Infect. Dis. **49**:297, 1931.

Nine cultures representing six species of Mycobacterium were found to contain no ergosterol when cultivated on 5 per cent glycerol nutrient agar. Unactivated ergosterol added to this medium was found to stimulate the growth and also the production of pigment by these cultures, whereas activated ergosterol showed no stimulation of the growth, but even a retarding of the growth in the higher concentrations used. The latter substance also stimulated the production of pigment. Pathogenic strains of Mycobacterium tuberculosis, both human and bovine, were more sensitive to activated ergosterol than the nonpathogenic strains of the same types.

AUTHORS' SUMMARY.

ACID-FAST MICRO-ORGANISMS. F. EBERSON and M. A. SWEENEY, J. Infect. Dis. **49**:303, 1931.

Cultivation in nonprotein mediums favored the loss of acid-fastness of a strain of tubercle bacilli. The strain was then avirulent and devoid of invasiveness in guinea-pigs and not allergic, and it failed to protect animals against a small dose of virulent culture. Lipoidal substances in culture mediums did not transform ordinary nonacid-fast bacteria into acid-fast types or alter the tinctorial characteristics of tubercle bacilli. The staining reaction of an acid-sensitive strain of tubercle bacilli was not affected by varying temperatures. Virulent acid-fast bacilli differed from avirulent acid-sensitive strains in their reaction to dyestuffs that constitute the reagents in the Ziehl-Neelsen acid-fast staining technic. Neutral fuchsin favored the development of acid-sensitive organisms in the avirulent strain. Tinctorial effects of other dyes seemed related inversely to the bactericidal action of given dilutions. Acid-fastness was a characteristic of organisms that resisted

the lethal action of concentrated solutions of the given dyes. The virulent strain H37 failed to grow in culture medium to which the same dyes had been added. The acid-fast variants in the avirulent strain of tubercle bacilli did not exhibit the same degree of sensitivity to environmental influences as the original acid-fast strain. A culture that had become acid-sensitive could not be readily converted into the original acid-fast type.

EDNA DELVES.

DOUBLE INFECTION BY THE BRUCELLA GROUP. C. F. JORDAN and I. H. BORTS, Pub. Health Rep. **46**:2437, 1931.

A Mexican laborer, aged 30, left his native country in February, 1930, took sick during April in Missouri, and was treated for undulant fever in a hospital in Iowa for thirty-two weeks. The blood culture yielded two strains of Br. melitensis — varieties melitensis and abortus. The melitensis variety of Brucella infection was in all likelihood acquired in Mexico because: (1) with this one exception, all of the cases of undulant fever in Iowa, so far as is known, have been due to Br. melitensis, variety abortus or suis, variety melitensis not being endemic in Iowa; (2) Br. melitensis, variety melitensis, infection is known to be endemic in Mexico; (3) the patient had contact with and used dairy products from goats in Mexico, but not in the United States. The source of the abortus variety of organism is not clear. A double infection may have developed before the patient left Mexico, as he used milk in addition to caprine dairy products. On the other hand, it is possible that the bovine infection was superimposed after the patient's arrival in Iowa. Pasteurized milk was used, but several cases of undulant fever are known to have occurred in the same community, with dairy products as the probable source of infection, one other case occurring within the same period.

AUTHORS' SUMMARY.

EFFECT OF HEMOLYTIC STREPTOCOCCI AND THEIR PRODUCTS ON LEUKOCYTES. A. EVANS, Pub. Health Rep. **46**:2539, 1931.

Leukocytes are injured by acid. If the injury is not too great, they may be restored to a healthy condition by bathing in blood serum. In filtrates of broth cultures of Streptococcus scarlatinae there is a trace of a substance toxic for leukocytes which can be detected by the bioscopic test, but not by the phagocytic test or by the deterioration of cells as shown in stained microscopic preparations. The addition of kidney tissue, blood serum or washed leukocytes to broth cultures does not increase the production of the leukocidic substance. On the other hand, the addition of washed erythrocytes to broth cultures definitely promotes its increase. The thermolability of the trace of leukocidic substance in filtrate of broth culture is the same as that of the more abundant leukocidic substance in filtrate of culture in broth plus erythrocytes. Presumably the two substances are identical. A specific neutralizing agent for the leukocidic substance could not be demonstrated in normal or immune serum. Two lines of evidence are offered to show that the leukocidic substance is identical with hemolysin; they differ in thermolability, and there is no correlation of toxicity for the two types of blood cells manifest by filtrates of cultures grown under varying conditions. The decrease of leukocidic substance in purified and concentrated skin toxin indicates that the leukocidic substance and skin toxin are not identical.

AUTHOR'S SUMMARY.

A NEW MEDIUM FOR DIFFERENTIATING FORMS OF DIPHTHERIA BACILLUS. J. ANDERSON, F. HAPPOLD, J. MCLEOD and J. THOMSON, J. Path. & Bact. **34**:667, 1931.

There are two principal forms of the diphtheria bacillus. B. diphtheriae-gravis is associated with severe toxic cases of the disease. It grows with granular deposit and pellicle in broth, has a flattened lusterless colony of irregular outline and

actively ferments polysaccharides. B. diphtheriae-mitis is associated with milder cases of disease in which there may be extensive membrane formation without serious intoxication, and which is probably chiefly dangerous from laryngeal involvement and obstruction of breathing. This form grows with uniform turbidity on broth, has a convex, partly translucent and light-reflecting colony and does not ferment polysaccharides. In addition, there have been observed from 5 to 10 per cent of intermediate forms giving granular growth in broth but failing to ferment starch, etc. The strain Park Williams 8 falls into this class. So far as they have been observed, the characters of these different forms are fixed. A blood agar medium is described, prepared with slightly heated broth sterilized by infiltration, and containing 0.04 per cent potassium tellurite, which permits determination of the presence or absence of B. diphtheriae at sight in 90 per cent of cultures from throat swabs after from eighteen to twenty-four hours of incubation. It also gives with the gravest types of diphtheria, those associated with B. diphtheriae-gravis, a picture so characteristic that it is not likely to be confused with anything else.

AUTHORS' SUMMARY.

EXPERIMENTAL STUDIES ON LYMPHOGRANULOMATOSIS. P. FOULON and P. LESBRE, Ann. d'anat. path. **8**:477, 1931.

The authors undertook to test Sternberg's assertion that Hodgkin's disease is of tuberculous origin. They used three methods of investigation: animal inoculation, cultures of tissues removed from patients, and biologic methods (Bordet-Wassermann, intradermal reaction, etc.). The results obtained show that "lymphogranulomatosis, at least in the cases observed by the authors, has nothing in common with tuberculosis."

B. M. FRIED.

MECHANISM OF EXPERIMENTAL TUBERCULOUS INFECTION. A. BOQUET, J. VALTIS and A. SAENZ, Ann. Inst. Pasteur **46**:373, 1931.

A careful study of the pathogenesis with regard to the guinea-pig indicates that the tubercle bacilli enter by way of the lymphatics, then into the blood stream and thus spread to the viscera. The rate of diffusion varies with the method of inoculation and with the number and virulence of the organisms. In massive infection, the bacteremia appears after an hour and persists until death. Progress is much slower with lighter inocula. Certain tissues, such as the pulmonary and serous parenchyma, owing to the extent of the surfaces and to the multiplicity of potential foci, are more affected than subcutaneous or submucosal connective tissue, accounting for the gravity of pulmonary, pleural or peritoneal infection, as compared to subcutaneous or digestive infection. From the fact that the grass bacillus invades in much the same manner as the tubercle bacillus, except in degree, it is concluded that the fatty structure is more involved than the actual pathogenicity. Actual virulence depends more on the ability to multiply in the tissues. Thus, with a slight infection with virulent organisms, the bacteremia may be so delayed that immunity offsets the effects. Localized foci develop, and latent infections may occur, as seen in naturally infected men and animals.

FROM AUTHORS' CONCLUSIONS.

NATURAL INFECTION OF THE RABBIT WITH TUBERCULOSIS. E. COULAUD, Ann. Inst. Pasteur **46**:424, 1931.

Tuberculosis in the rabbit is of frequent occurrence, but it is often a latent infection that may show a spontaneous cure. Such tuberculous animals may not respond to tuberculin tests. Infection appears to occur during natural exposure or association with tuberculous animals. Most of the lesions noted were pulmonary, at times massive and progressive, often small, tuberculous nodules.

M. S. MARSHALL.

PATHOLOGIC ANATOMY OF RABBITS INOCULATED WITH B C G. D. D. LOKHOFF and I. K. LEVITAN, Ann. Inst. Pasteur **47**:45, 1931.

Forty animals were divided into three groups. The first received B C G by intravenous or intraperitoneal routes, the second received virulent organisms intravenously, and the third received human tubercle bacilli intravenously followed by B C G (intravenously or subcutaneously) after five or more weeks. The average survival of treated animals exceeded that of the controls by fifty-three days, and the incidence of grave lesions was greatest in the control animals. On the injection of B C G, the progress of tuberculous processes is appreciably moderated, varying in degree with the route of inoculation. The tissues show distinct differences. The lungs of treated animals show proliferation of the connective tissue around the tubercles, and islets of caseous pneumonia in the form of diffuse sclerosis, points lacking in controls animals. Cicatrization is complete, and calcification of the caseous masses seems to occur more frequently. The spleens of the animals used as controls were normal; in the treated animals this organ usually showed hypertrophy and hyperplasia and hypertrophy of the cellules, suggesting mobilization in the reticulo-endothelial system. Other lesions were not distinctive. A marked inflammatory response of the lesions, as follows after the injection of tuberculin, was not observed.

M. S. MARSHALL.

Immunology

NATURE OF ANAPHYLAXIS. DESPLANQUES, SIMONNET and VERGE, Ann. Inst. Pasteur **47**:332, 1931.

"The potency of horse serum in inducing the anaphylactic shock in the guinea-pig seems uniquely bound to the globulin fraction; the serin appears to be an inactive albumin from the point of view of anaphylaxis of this species."

THE PRODUCTION OF ANTITOXIN ON THE ADDITION OF NONSPECIFIC SUBSTANCES TO THE ANTIGEN. G. RAMON, Ann. Inst. Pasteur **47**:339, 1931.

In the course of weekly tests of antidiphtheria serum from a number of horses, it was noted that certain animals suddenly produced serums of especially high titer. The explanation was found in the previously reported fact that abscesses had developed at the points of injection of the toxin. This increase in the production of antibodies could be provoked at will by introducing nonspecific material with the antigen (powdered tapioca and calcium chloride proved the most satisfactory). By this means, the production of antitoxin by all animals could be increased, and adequate production could be secured in exhausted animals provided they were in good general condition. Similar results were obtained in immunization against tetanus. The principle is being applied to man. Diphtheria anatoxin is combined with typhoid vaccine, mixed in equal parts, and injected in 1, 2 and 3 cc. amounts at fifteen day intervals, to increase the effectiveness of the former. The results are said to have been excellent.

A. F. DEGROAT.

EVOLUTION OF DIPHTHERIA ANTIBODIES IN HORSES. A. BESSEMANS, G. RAMON and F. DE POTTER, Ann. Inst. Pasteur **47**:358, 1931.

Subcutaneous injections of either toxin or living diphtheria bacilli into horses lead only to the production of antitoxin. No agglutinins are noted. Intravenous or intraperitoneal injections of living bacilli cause a transitory production of antitoxin, but specific agglutinins appear in abundance. The quantity of complement is variable and is independent both of the method of immunization and of the agglutinin and antitoxin titers of the serum. Thus, the evolution of antibodies is the result, not only of the type of antigen used but also of the method of injection. Estimations of the degree of immunity to diphtheria may best be based solely on antitoxin titer. The authors hold that their data support the hypothesis of the multiplicity of antibodies.

A. F. DEGROAT.

B C G Vaccine. H. Buschmann, Ann. Inst. Pasteur **47**:374, 1931.

Children vaccinated by mouth with B C G vaccine showed 76 per cent positive reactions to B C G tuberculin intracutaneously. Subcutaneous vaccination resulted in 86 per cent positive tests. When the Pirquet test was used, the figures were respectively 61 and 63 per cent. Neither change in virulence, nor dissociation, nor adverse reactions were observed in the study of the vaccine.

From the Author's Conclusions.

Lesions in Tuberculous Guinea-Pigs Treated with B C G. Levitan and Lokhoff, Ann. Inst. Pasteur **47**:484, 1931.

Gross and histologic examinations were made of 130 guinea-pigs, inoculated with B C G between the twenty-ninth and the one hundred and eighty-ninth days of tuberculous infection. Besides two control groups, 79 animals were given human tubercle bacilli, principally intraperitoneally, followed by 0.002 and 0.0002 mg. of B C G subcutaneously every fourteen days. Macroscopically, 20 showed grave, 39 average, and 20 few lesions, very much as in the control groups. Microscopically, a difference both in the frequency and in the degrees of fibrosis was noted in the bronchial lymph nodes. It is concluded that, once the infection has started, B C G has little effect on the development of tuberculosis, but that the animals survive on the average twice as long. The reasons are apparent only microscopically: caseous or purulent pneumonic forms are rare; in the lungs and in the liver an interstitial inflammation is frequent; the spleen shows a more intense reaction of the reticulo-endothelial system; sclerosis and calcification of the lymph nodes are regularly noted.

M. S. Marshall.

Paralysis Following Prophylactic Treatment for Rabies. S. G. Moftah and M. S. Nabih, Office intérnational d'hygiène publique **23**: 2007, 1931.

Over a period of twenty years, 27,060 persons received antirabic treatment. The few cases of paralysis that developed were benign. Then, within two years, there were several deaths. Thirteen cases of paralysis varied in severity from a slight facial palsy to a Landry syndrome. All the patients in this group recovered. One, a laboratory worker, had been vaccinated yearly without ill effects, and then suffered a generalized paralysis after two successive treatments. In eight cases, the symptoms were those of acute myelitis. This diagnosis was confirmed at autopsy in four. In one case the cervical and in three the lumbar, enlargement of the cord was involved. These segments were hyperemic and edematous, and microscopically there were degenerations of nerve cells and fibers with widespread perivascular mononuclear infiltration. No Negri bodies were found in the brain, and animal inoculations were negative. Because animal inoculations were negative, and because one patient had received the phenolated vaccine, the authors conclude that the paralysis was due neither to the fixed nor to the street virus. They can suppose only that the vaccine contains a toxin. According to Babès, the toxicity of fixed virus sometimes increases after passage through a guinea-pig. The deaths reported occurred, in fact, shortly after two such passages.

Albert F. DeGroat.

Immunization of Guinea-Pig Spleen Against Tetanus Toxin in Tissue Cultures. M. Toyoda, Arch. f. exper. Zellforsch. **10**:463, 1931.

Cultures of the spleen kept for some time in a medium containing tetanus toxin acquire the quality to tolerate considerably higher doses of toxin than would be lethal to normal cells.

Wilhelm C. Hueper.

THE ALLERGIC REACTION IN TUBERCULOUS INFECTION: ITS ANATOMIC ASPECT. P. SCHWARTZ and R. BIELING, Verhandl. d. deutsch. path. Gesellsch. **26**:226, 1931.

Rabbits the testes of which were infected with human tubercle bacilli were three weeks later inoculated intravenously with bovine tubercle bacilli. A few of these animals died from shock in the first days after the reinfection. Anatomically, there were noted pulmonary edema, splenic tumor with extensive cellular necrosis and necrosis of hepatic cells. In the rabbits that survived the second infection for from two to ten days, parietal intravenous granulomas were observed in the walls of the veins in the lungs and liver. They resembled the nodules described by Siegmund in scarlet fever. In animals killed from four to ten days after reinfection, the heart muscle showed smaller and larger nodules that looked like Aschoff's bodies in rheumatism. Also in rabbits that died from a single intravenous injection of bovine tubercle bacilli, identical anaphylactic morphologic changes were noticed, namely, hepatic necrosis, acute splenic tumor and inflammatory pulmonary edema. These lesions are explained by a spontaneous hematogenous reinfection with tubercle bacilli in the sensitized organism.

C. ALEXANDER HELLWIG.

REACTION OF THE LYMPHOID TISSUES TO ACTIVE IMMUNIZATION. T. HELLMANN and G. WHITE, Virchows Arch. f. path. Anat. **278**:221, 1930.

A series of twenty-three rabbits, divided into four groups according to their ages, were actively immunized by intravenous injections of a killed strain of Bacillus paratyphosus B. From one to five injections were made in periods of from three to sixty-four days. The lymphoid tissues were removed and studied by a method previously described by Hellman, by which nine tenths of the lymphoid tissue of the animal is subjected to examination. The chief effect of the process of immunization was noted in the spleen. This organ was enlarged, the enlargement being due to well marked hyperplasia of the germinal or reaction centers of the lymphoid follicles and of the white pulp and, to a lesser degree, to hyperplasia of the red pulp. The rest of the lymphoid tissues participated in the reaction, but not to so great an extent as the spleen. Increase in the size and number of the reaction centers of the lymphoid follicles is due to reticuloendothelial hyperplasia, the hyperplasia being the result of stimulation by the process of immunization. The lymphoid tissues, through their reticuloendothelial components, play an important part in the development of the immune state.

O. T. SCHULTZ.

THE RELATIONSHIP BETWEEN BACTERICIDAL ACTION OF THE BLOOD AND COAGULATION-INHIBITING SUBSTANCES. JORG KOSCHATE, Zentralbl. f. Bakt. (Abt. 1) **118**:60, 1930.

The immediate dilution of blood in ten parts of a 4 per cent solution of sodium citrate gave the highest colony counts from patients whose blood contained staphylococci, streptococci, paratyphoid bacilli and typhoid bacilli. The citrate solution was distinctly superior to heparin, bile, broth, potassium oxalate or magnesium hydroxide. Comparative experiments with these substances, Staphylococcus aureus and Streptococcus hemolyticus also showed the least bactericidal effect in the citrate-blood-bacteria mixture. The author attributes the favorable effect to the better inhibition of blood-clotting.

PAUL R. CANNON.

THE EFFECT OF ORAL IMMUNIZATION ON THE FORMATION OF HUMORAL ANTIBODIES. R. PFEIFFER and H. LUBINSKI, Zentralbl. f. Bakt. (Abt. 1) **118**:152, 1930.

Oral administration to rabbits of killed cultures of cholera spirilla led to extremely minute formation of humoral antibodies, although intravenous injec-

tions of similar dosages gave a large yield. The authors believe that the production of antibodies following oral administration may be due to the passage of antigen through small lesions in the intestinal mucosa. Nevertheless, the results of the parenteral administration were 75,000 times better than those of the enteral, as measured by concentration of humoral antibodies.

Even poorer results were obtained in human beings treated with typhoid bacilli, only traces of antibodies being found in the serum following oral administration of the antigen.

If the presence of bactericidal and agglutinating substances in the serum is considered the criterion of immunization, oral administration gives no results indicating immunization.

PAUL R. CANNON.

PASSIVE IMMUNIZATION WITH HERPES ANTISERUM. HELMUTH FREUND, Zentralbl. f. Bakt. (Abt. 1) **119**:20, 1930.

The author obtained antiserum for herpes by injecting a nonlethal dose of the virus intracorneally. Reinjections were made in the same or in the opposite eye. The serums of such animals contained viricidal properties to a titer of 1:25.

The intravenous injection of such serums protected rabbits against spontaneous encephalitis after corneal injection of the virus, but had no influence in healing an existent herpes encephalitis.

Guinea-pigs previously treated with several doses of the rabbit antiserum were almost completely protected against the herpetic infection produced intracutaneously. Normal rabbit serum had no such effect.

PAUL R. CANNON.

IMMUNOLOGIC RELATIONSHIPS BETWEEN HERPES AND VACCINIA. HELMUTH FREUND, Zentralbl. f. Bakt. (Abt. 1) **119**:25, 1930.

Freund treated guinea-pigs intraperitoneally on five or six successive days with about 1 cc. of herpes antiserum obtained from rabbits infected intracorneally on several occasions with the virus. The guinea-pigs were then given intracutaneously, together with controls, vaccine virus, all injections being made into the plantar skin. The vesicles that developed were smaller and less well filled and showed a sharper line of demarcation in the serum-treated animals than in the controls. They also dried up more quickly in the former animals. These experiments confirm those of Gildemeister and his collaborators.

PAUL R. CANNON.

A HISTAMINE-LIKE SUBSTANCE IN RYE POLLEN (SECALE CEREALE). C. E. BENJAMINS, Ztschr. f. Immunitätsforsch. u. exper. Therap. **72**:189, 1931.

Extracts of rye pollen had a histamine-like effect on uteri of guinea-pigs and cats tested with the Dale technic, producing contractions in previously sensitized and nonsensitized animals. The substance is thermostable; it is resistant to the action of digestive ferments; it passes a dialyzing cellophane membrane under pressure. In the skin of healthy persons, it produces reactions identical with those called forth by histamine, with which it has also in common the effect on the blood pressure and iris of cats and rabbits, and on the chromatophores of the frog's skin. The substance in question is physiologically identical with histamine. No such substance could be detected in the following Gramineae: Holcus mollis, Festuca rubra, Cynosurus cristus, Alopecurus pratensis, Phleum pratense, Dactylis glomerata and Lolium perenne.

I. DAVIDSOHN.

THE INFLUENCE OF EXHAUSTION ON ANTIBODY PRODUCTION AND ON THE COURSE OF INFECTION. E. FRIEDBERGER, O. ANDERSEN, C. CALLERIO and I. RUTCHKO, Ztschr. f. Immunitätsforsch. u. exper. Therap. **72**:225, 1931.

Running, leading to complete exhaustion, had no effect on the titer of complement in guinea-pigs, on the normal antisheep hemolysin in rabbits, or on the

development of antisheep hemolysin and of bacterial agglutinins in immunized rabbits. Exhaustion did not seem to influence the course and outcome of the disease in rats infected with El Tor.

I. DAVIDSOHN.

THE PURIFICATION OF DIPHTHERIA TOXIN AND ANATOXIN. I. A. TASMAN and A. B. F. A. PONDMAN, Ztschr. f. Immunitätsforsch. u. exper. Therap. **72**: 245, 1931.

A comparative review of the methods used for purification and concentration of diphtheria toxin and anatoxin, with selection of the "Alum-method," for which a detailed procedure is outlined. The end-product, which is a toxin and not a toxoid, is not as durable as the original solution.

I. DAVIDSOHN.

A LOCAL SKIN REACTION WITH EXTRACTS OF PROTEUS X19 (THE EXANTHIN REACTION). LUDWIG FLECK, Ztschr. f. Immunitätsforsch. u. exper. Therap. **72**:282, 1931.

Guinea-pigs infected with Rickettsia prowazeki lost the normal cutaneous reactivity to the extracts after about five to ten days following the onset of the illness. This lack of reactivity was specific, as extracts of Proteus vulgaris called forth the normal response. In rabbits, the same behavior was observed but only after from four to six weeks following infection. In rabbits immunized with Proteus X19, the cutaneous reactivity disappeared after about four to six months of immunization; they showed a somewhat increased resistance to infection with Rickettsia prowazeki. Rabbits immunized with killed Rickettsia prowazeki lost their cutaneous reactivity to Proteus X19. The Proteus X19 extracts could not be neutralized with a homologous rabbit immune serum, while such neutralizations sometimes occurred with typhus fever convalescent serums of man and guinea-pigs. Cutaneous hypersensitivity and hyposensitivity could sometimes be passively transferred. A close relationship and possible identity of Rickettsia prowazeki and of Proteus X19 is suggested by the results of the experiment.

I. DAVIDSOHN.

THE WASSERMANN REACTION FOLLOWING IMMUNIZATION WITH SPIROCHAETA PALLIDA. M. P. BATUNIN and R. R. HÖLTZER, Ztschr. f. Immunitätsforsch. u. exper. Therap. **72**:326, 1931.

This problem, repeatedly attacked in recent years, was here approached with somewhat different technic: (*a*) using various routes for injections, (*b*) prolonging the period of immunization, and (*c*) injecting guinea-pigs with living spirochetes. The results in guinea-pigs were perfectly negative; their serum did not react with alcoholic extracts of the spirochetes or with the usual organ extracts. In man, serums were obtained that showed a very weak fixation of complement with alcoholic extracts of the spirochetes and only transient inhibition of hemolysis with the other extracts. The method of immunization and the quantity of the injected antigen had no bearing on the serum response.

I. DAVIDSOHN.

THE CHEMICAL NATURE OF SO-CALLED SYPHILIS ANTIGENS. ÖDÖN FISCHER, Ztschr. f. Immunitätsforsch. u. exper. Therap. **72**:344, 1931.

Treating cholesterol-free phosphatides of beef heart with aluminium hydroxide ($Al[OH]_3$) and with calcium phosphate ($Ca_3[PO_4]_2$) removed their ability to act as antigens in complement-fixation and precipitation tests for syphilis. The change was not due to a decrease in the contents of the phosphatides and fatty acids or to a change in their relative proportions. Addition of fatty acids or of cholesterol did not effect reactivation of the extracts. Kaolin and barium sulphate ($BaSO_4$) did not influence the antigenic properties of phosphatides of beef heart or had only a very slight effect.

I. DAVIDSOHN.

ALCOHOLIC EXTRACTS OF BACTERIA IN THE FIXATION TEST FOR SYPHILIS. HERMANN DEBUS, Ztschr. f. Immunitätsforsch. u. exper. Therap. **72**:373, 1931.

Lecithin increased the antigenic efficiency and removed the anticomplementary action of alcoholic extracts of tubercle bacilli in relation to homologous antiserum and syphilitic serum. Proper quantitative relations between the extracts and the lecithin and proper technic in diluting the mixture with saline solution were important. The antigenic efficiency approached, but did not equal, that of cholesterolized beef extract. Mixtures of lecithin and of alcoholic extracts of diphtheria bacilli and of colon bacilli fixed complement with syphilitic serum but less efficiently than extracts of tubercle bacilli.

I. DAVIDSOHN.

EVALUATION OF SCARLET FEVER ANTISERUMS BY BLANCHING. F. V. BORMANN and A. WOLFF-EISNER, Ztschr. f. Immunitätsforsch. u. exper. Therap. **72**: 411, 1931.

By comparative tests with various dilutions of different serums on the same patients the conclusion is arrived at that there is a direct relation between the ability of the serum to produce blanching of the cutaneous eruption and its therapeutic efficiency. Besides the dilution of the serum, the intensity and duration of the local effect must also be considered. The blanching phenomenon is due to a local antitoxic effect. (See articles by same authors on the blanching phenomenon in *Ztschr. f. Kinderh.* **51**:550 and 560, 1931.)

I. DAVIDSOHN.

BIOLOGIC DIFFERENTIATION OF MEAT BOILED FOR A LONG TIME. HERMANN RODENBECK, Ztschr. f. Immunitätsforsch. u. exper. Therap. **72**:482, 1931.

The antigen used for the preparation of the precipitating serum consisted of a mixture of chicken meat and an extract of the meat obtained by treating it with saline solution and subsequently with sodium hydroxide. An immune serum prepared with this antigen precipitated extracts of meat boiled for a long time, while the usual precipitating immune serums failed to do so. With the help of such a serum it was possible to establish the presence of chicken meat in the commercial preparations of chicken bouillon. Complement-fixing antibodies could not be demonstrated. An attempt to produce specific precipitating serums with meat extracts failed.

I. DAVIDSOHN.

THE THERMOSTABILITY OF ANTIBODIES. LEO OLITZKI, Ztschr. f. Immunitätsforsch. u. exper. Therap. **72**:498, 1931.

Dilution of immune serums to 1:100 protected the antibodies against the effect of heat equally well as the treatment with Bayer 205, with glycerin and with certain buffers as suggested by L. Silber, and had a wider range of applications. Protein-free antibody solutions, prepared according to M. Frankel and L. Olitzki, showed a marked resistance to heat of a character similar to that of diluted immune serums; treatment with Bayer 205, glycerin, etc., did not further increase their thermoresistance. The destruction of antibodies by heat is due to two factors: (*a*) coagulation of the proteins (in concentrated serums)—the coagulated particles take down the antibodies with them—and (*b*) direct destruction by heat (in highly diluted serums). This is well exemplified by the following experiment: Some of the agglutinins in a typhoid immune serum diluted 1:10, which were lost by heating, reappeared following treatment with hydrochloric acid and pepsin. The latter liberated the antibody by digesting the coagulated protein particles. The antibody destroyed by heat in a 1:100 dilution of the immune serum could not be regained by the digestive action, its disappearance being here due to the direct action of the heat.

I. DAVIDSOHN.

THE IMMUNOLOGIC RESPONSE OF SYPHILITIC RABBITS TO LIPOIDS. LUDWIG PRÜSENER, Ztschr. f. Immunitätsforsch. u. exper. Therap. **72**:515, 1931.

The frequently reported positive Wassermann reaction found for normal rabbits is due to an improper technic. With the author's technic the reaction was regularly negative. Rabbits were treated with cow's milk, goat's milk, a non-specific milk preparation, an aqueous extract of guinea-pig kidney, an extract of the spirochetes of syphilis, and an aqueous extract of syphilitic rabbit testicles. Some of these rabbits were previously infected with syphilis, and their positive Wassermann reaction became negative. None of them developed a true positive Wassermann reaction, i. e., the ability to fix complement in the presence of alcoholic tissue extracts commonly used as antigens in the Wassermann test. Treatment with a mixture of lecithin and hog serum led to the development of positive Wassermann and Meinicke reactions, the latter appearing earlier than the former. The reagins so produced did not disappear after injections of arsphenamine nor could they be removed from the serum by the Sachs method.

I. DAVIDSOHN.

Tumors

SARCOMA OF THE SPLEEN. LOUIS FRANK, Am. J. M. Sc. **183**:77, 1932.

Here have been added to the literature reports of two cases of sarcoma of the spleen, both being cases of the lymphocytic type. Sarcoma of the spleen may simulate pernicious anemia in its symptomatology and hemocytology.

AUTHOR'S SUMMARY.

BENIGN TUMORS OF THE BRONCHUS. H. WESSLER and COLEMAN B. RABIN, Am. J. M. Sc. **183**:164, 1932.

Based on a study of seventeen cases, we have sought to define a clinical picture of benign tumors of the bronchus. Our study has been concerned mainly with adenoma, which appears to be the commonest type of tumor encountered clinically. The following facts are emphasized: Care must be exercised in the microscopic diagnosis of these tumors lest they be mistakenly regarded as malignant. Benign tumors of the bronchus probably have a long period of latency during which there may be no symptoms of bronchial obstruction or bronchial irritation. In a considerable percentage of the cases this period is characterized by repeated hemorrhages. Aside from the symptoms of bronchial obstruction and infection, pulmonary hemorrhage is a frequent symptom of adenoma of the bronchus. This bleeding has certain characteristics that may suggest the diagnosis. When stenosis of a bronchus with infection of a lung has occurred, the clinical picture may be confusing. These clinical pictures are described. The prognosis of benign tumors of the bronchus depends on the early discovery and removal of the tumor, which may lead to prompt cure. When secondary inflammatory changes have occurred in the lung, the outlook is not good. Evidence is adduced which indicates that polypoid adenomas may undergo malignant degeneration.

AUTHORS' SUMMARY.

MELANOMA OF THE MENINGES. N. C. FOOT and P. ZEEK, Am. J. Path. **7**:605, 1931.

Two cases of melanoma, presumably primary in the meninges, are described. In one of them, a small primary tumor was shown in the choroid plexus with a copious petechial metastasis throughout the meninges of the brain and cord; the other was striking because of the presence of two good-sized tumors in the meninges, with metastasis to the lungs, a very unusual event in the case of cerebral tumors. It is believed that the facts brought out in the study of these cases point strongly to the validity of Masson's argument as to the origin of melanoma

in the nervous system; these tumors had nothing to do with the skin, so far as we could ascertain, and they showed the presence of fibrils that could only with difficulty be interpreted as representing anything but fibrils in some way connected with peripheral nerves.

AUTHORS' SUMMARY.

ON THE SILVER IMPREGNATION OF MELANOTIC TUMORS. N. C. FOOT, Am. J. Path. **7**:619, 1931.

The microscopic examination of material from normal skin and mucosa, a variety of nevi and several melanoblastomas by means of a thoroughly reliable silver impregnation seems to bear out Masson's theory as to the relationship of pigmented moles and their malignant relatives to the nervous system. That the "Merkel-Ranvier," or "nevus" cell, divisible into tactile cells of various sorts, and the cells of the nonmedullated nerve fascicula all represent various phases in the life of one cell type in these tumors seems fairly evident, if not proved. That these cells may take the form of scattered individuals, nests resembling Meissner corpuscles, melanoblasts or neurofibromatoid complexes seems clear. In malignant tumors, it is only natural to expect more or less atypical growth and anaplasia and a return to structures representing stages in the fetal development of the cell. Alveolar and gland-like structures seen in "melanocarcinomas" should not, therefore, prove to be a very disturbing note in the theory. The silver impregnation as a means of recognizing and classifying these tumors cannot be too highly recommended; it is simple in operation, and experiment proves that it can be successfully carried out at the first attempt. It is to be regretted that it cannot, as yet, be successfully applied to paraffin sections, but as experiments are now under way, this difficulty may be solved. The striking difference between the epidermal and the nevus cells, when impregnated by this method, is at once evident, the association of fibrils with the latter afford a reliable criterion that is immediately applicable. In closing, it would not be trite to reiterate Masson's warning to investigators along these lines: Please do not rely on old, wornout methods while endeavoring to check up on this theory, but use those that Masson has perfected, or the one herein described.

AUTHOR'S SUMMARY.

MASSIVE UNATTACHED RETROPERITONEAL TUMORS. G. H. HANSMANN and J. W. BUDD, Am. J. Path. **7**:631, 1931.

Seventeen retroperitoneal tumors that were not attached to adult urogenital organs are reported. All the tumors were similar to tumors that arise in the adult urogenital organs. Studies of retroperitoneal tumors collected from the literature integrated with the material of this paper have shown that almost all tumors that occur in adult urogenital organs may occur free along the course of development of the urogenital apparatus. The concept that they arise from remnants of the urogenital apparatus is the most logical explanation of their histogenesis.

AUTHORS' SUMMARY.

PAPILLIFEROUS TUMORS OF THE THYROID GLAND AND OF ABERRANT THYROID TISSUE. A. R. MORITZ and F. BAYLESS, Am. J. Path. **7**:675, 1931.

One hundred and two papilliferous tumors of the thyroid gland or of aberrant thyroid gland tissue were studied and classified. Twenty-eight of these were from the Institute of Pathology of Western Reserve University and seventy-four were studied in published case reports from other courses. The differential characteristics of the various types are tabulated. These characteristics were not invariably present, but were the most commonly present. The papilliferous character of adenomas and malignant adenomas did not distinguish them from the non-papilliferous forms of those tumors so far as growth was concerned, while the

papilliferous cystadenomas and cystadenocarcinomas constituted a group of tumors having peculiar and characteristic growth. The term "papilliferous" as applied to tumors of the thyroid gland is significant only in connection with papilliferous cystadenomas and papilliferous cystadenocarcinomas.

AUTHORS' SUMMARY.

MYELOMA WITH UNUSUAL AMYLOID DEPOSITION. B. H. PAIGE, Am. J. Path. **7**:691, 1931.

A case of multiple myeloma is reported with an associated extensive amyloidosis. Of interest, both clinically and pathologically, are the huge tumor-like masses that resulted from the deposition of amyloid in the striated muscles and about the shoulder joints. Worthy of note, also, are its presence in the spleen, kidneys, suprarenal glands, gastro-intestinal tract, heart, pancreas, reproductive organs, sympathetic ganglions and adipose tissue and its absence from the parenchyma of the liver.

AUTHOR'S SUMMARY.

TUMORS OF THE ISLANDS OF LANGERHANS AND HYPOGLYCEMIA. M. G. SMITH and M. G. SEIBEL, Am. J. Path. **7**:726, 1931.

Pancreatic tumors producing hypoglycemia are composed largely of abnormal beta cells. In cases of hypoglycemia due to a pancreatic tumor of island tissue, the normal island cells are not overstimulated. From anatomic studies in these cases there is no evidence that the activity of the normal island cells is depressed, although clinical studies of the sugar tolerance suggest this in some cases. Adenomas resembling islands of Langerhans in their cellular arrangement, which give neither clinical nor anatomic evidence of functional activity, may occur. Adenomas of the islands of Langerhans are not rare; even those with clinical symptoms are surprisingly frequent.

AUTHORS' SUMMARY.

PLACENTOMA IN YOUNG RATS AFTER GONADAL STIMULATION. M. C. SHELESNYAK, Am. J. Physiol. **98**:387, 1931.

Fresh extracts of beef anterior pituitary lobe were injected daily into young rats, and after four or five days the uteri were stimulated by threading. The injections were continued, and the animals examined on the third to the fifth day after this operation. With great uniformity, they showed deciduomatous nodules. Controls, in which a commercial extract of the pituitary gland was used instead of the fresh extract, failed to show these results.

H. E. EGGERS.

THE INFLUENCE OF HEREDITY ON THE OCCURRENCE OF CANCER IN ANIMALS. H. G. WELLS, Ann. Int. Med. **4**:676, 1931.

The study of animals has shown beyond any question of doubt that heredity plays a great rôle in determining not only whether animals will or will not develop cancer, but also what the type and location of the neoplasm will be. It has also been established that heredity may determine whether cancer will or will not arise from a fairly constant type of injury. As demonstrated by Loeb and others, the combination of the genetic background with the stimulation is the essential factor in the production of cancer. The observations of Slye would appear to indicate that susceptibility to cancer behaves as a mendelian recessive, and that resistance to cancer is dominant. The study of transplanted tumors in animals indicates that they obey laws different from those obeyed by the spontaneous tumors of these animals. Histologically, the spontaneous neoplasms of animals present the same characteristics of growth as similar neoplasms present in human beings.

WALTER M. SIMPSON.

HEREDITY OF CARCINOMA IN MAN. A. S. WARTHIN, Ann. Int. Med. **4**:681, 1931.

There would appear to be in some human families a dominant inheritance of the cancer factor, while in other families this factor manifests itself as a recessive inheritance. The great variation in susceptibility found in different members of the same family may possibly be explained by the great complexity of the cancer character. It cannot be a single, simple mendelian character, but may consist of a combination of a large number of factors. It is uncertain that in man the inheritance of susceptibility to cancer is always mendelian. From the available evidence we are certain of two factors: constitutional susceptibility to neoplasm and local predisposition of the organ to cancer. The first determines that a man may develop cancer; the second determines the organ or tissue involved. An important fact in proof of the hereditary nature of susceptibility to cancer is the occurrence of symmetrical neoplasms in members of the same family. If constitutional predisposition and organic predisposition to cancer are necessary to the development of a cancer, we should expect to find in identical twins examples of neoplasms affecting the same organ and the same part of the organ. This is precisely what has been observed in a number of cases.

From a proper interpretation of the influence of heredity of cancer in man it is necessary to consider at least four hereditary factors: the normal constitution resistant to blastoma; the pathologic constitution susceptible to blastoma; the normal resistant organ or tissue make-up, and the pathologic organ with cancerous predisposition. Each of these factors must be composite; no one is a simple unit factor in the mendelian sense. Each one represents large and complex genes in which a hundred or a thousand subsidiary factors may enter, which may mendelize independently or in combination. The old conceptions of dominant and recessive have lost their original significance as far as the inheritance of neoplasm in man is concerned. The possibilities of inheritance in the almost endless combinations that may result, the effect of diluent or intensifying combinations, the occurrence of lethal factors and their combinations, the action of the extrinsic factors of the environment and other modifying factors make the problem of the inheritance of carcinoma in man one beyond mathematical computation or prediction. The conception of mendelism that led Maud Slye to regard the inheritable susceptibility to tumor as a simple recessive unit character is all too primitive. Characters that show a dominant inheritance in several generations may be so modified that they thereafter show a recessive inheritance. Theoretically, the laws of Mendel have added much to the understanding of heredity, but their practical application in human heredity is limited because of the complexity of the problem.

WALTER M. SIMPSON.

GLAND EXTRACTS IN EXPERIMENTAL CARCINOMA AND SARCOMA OF ALBINO RATS. O. M. GRUHZIT, Ann. Int. Med. **4**:1589, 1931.

Albino rats inoculated with Flexner-Jobling carcinoma, when treated with different extracts of suprarenal cortex, both with high and low epinephrine content, showed neither delay nor regression in the growth of the tumors as compared with untreated tumor-bearing rats or those treated with a nonspecific protein extract of ox testis. Similar negative results were obtained with extracts of thymus. Extracts of suprarenal cortex, thymus, omental lipoid and ox testis neither inhibited growth nor caused regression of Jensen sarcoma in albino rats.

WALTER M. SIMPSON.

Medicolegal Pathology

POISONING OR SUDDEN NATURAL DEATH? F. NEUREITER, Beitr. z. gerichtl. Med. **11**:32, 1931.

Two apparently healthy men, 50 and 56 years old, respectively, entered a coffee house and ordered coffee and rolls. After one of them drank half a cup, he suddenly fell to the floor, dying instantly. His friend called for the ambulance.

About five or ten minutes later, the second man suddenly became pale and drawn, and fell over dead. The coffee and rolls were examined chemically, but no evidence of a poison was found. The autopsy in the first case revealed a marked occlusion of branches of the coronary arteries, with many myocardial scars and marked thinning of the posterior wall of the left ventricle. There was no evidence of poison either in the content of the stomach or in the other organs. The autopsy in the second case revealed a hypertrophied heart, with aneurysmal dilatation of the anterior wall of the left ventricle and marked calcification of the coronary arteries. In addition, many old fibrous scars were found in the myocardium. The mouths of both coronaries were encroached on. The ascending aorta showed syphilitic aortitis. The content of the stomach and the various organs in this case were also examined chemically and revealed no traces of poison. The author states that the peculiar coincidence of the sudden death of the two friends in such a short interval could at first give rise to the suspicion of homicide and suicide. The autopsies, however, revealed that the sudden death of both was due to natural causes.

O. SAPHIR.

A RARE CAUSE OF SUDDEN DEATH: PRIMARY SCLEROSIS OF THE PULMONARY ARTERY IN A 12 YEAR OLD GIRL. F. PUNTIGAM, Beitr. z. gerichtl. Med. **11**:106, 1931.

Sudden death of a 12 year old girl was the reason for a special investigation. Autopsy revealed marked arteriosclerosis of the pulmonary artery, with many small, yellow, circumscribed intimal thickenings, especially pronounced in both main branches. These branches were dilated and in some portions covered by mural thrombi, which were so large as to narrow their lumina markedly. The main pulmonary artery and the smallest branches showed no changes. In the course of the right pulmonary artery, several saclike dilatations were found. These dilated areas were filled with thrombi. Histologically, each of the larger branches of the pulmonary arteries showed a markedly thickened intima, which in places was twice as thick as the media. It consisted of a new formation of loose connective tissue. The internal elastic membrane was split in places, and the boundary between the media and the intima was not marked. The media also revealed a splitting of the intima and a new formation of connective tissue, with deposits of lime salts. Occasionally, small round cell infiltrations were noted in the media. The adventitia showed a perivascular infiltration by round cells. Regressive changes were not found. The heart was somewhat larger than normal. The right ventricle was larger than the left, dilated, its wall measuring 10 mm. in thickness, while the left ventricle measured 7 or 8 mm. The myocardium was normal. The ductus arteriosus was closed. The coronary vessels showed no changes. The peritoneal cavity contained 1,000 cc. of clear liquid. The liver, spleen and kidneys revealed marked chronic passive hyperemia.

The history which was obtained after the autopsy revealed that the patient had otitis media when she was 9 months old. At the age of 3, there was noted for the first time a disease of the circulatory apparatus, which increased in later years. Cyanosis was always marked thereafter. There was no edema or anasarca until a half year before death. Bloody sputum was often observed. The opinion is expressed that the otitis media had produced chronic inflammation of the pulmonary artery, which primarily was hypoplastic.

O. SAPHIR.

Society Transactions

BUFFALO PATHOLOGICAL SOCIETY

Regular Meeting, Feb. 12, 1932

KORNEL TERPLAN, *President, in the Chair*

SYSTEMIC RETICULO-ENDOTHELIAL PROLIFERATIONS WITH TUMOR-LIKE FORMATIONS IN A CASE OF CHRONIC LYMPHATIC LEUKEMIA. J. LOESCH.

During the last few years several reports have been published dealing with the proliferation of the reticulo-endothelial cells in various pathologic conditions. An additional case of unusual systemic proliferation with tumor-like formations is described.

The patient, about 47 years of age, a seaman, was admitted to the Buffalo City Hospital on July 1, 1931. He complained of shortness of breath, edema of the extremities and a sensation of pressure in the left upper quadrant of the abdomen. From the past history it was learned that he had a positive Wassermann reaction in 1925 when he applied for a position as a food-handler; thereafter, vigorous antisyphilitic treatment was given until 1929, consisting of several courses of arsphenamine, bismuth and mercury and one malaria treatment of ten chills; all of this, however, was without any effect on the positive Wassermann reaction. In 1931, the patient noticed for the first time a mass in the left axilla. At the time of admission, on July 1, 1931, he presented general enlargement of all the lymph nodes; the spleen was palpable and extended a hand's breadth below the costal margin; the lower extremities were markedly edematous. The red blood cell count was 3,655,000; the hemoglobin was 56 per cent (Sahli). The white cell count was 760,000. A differential count showed 100 per cent lymphocytes; occasionally a cell much larger than a normal lymphocyte was seen, with three nucleoli. The diagnosis was: chronic lymphatic leukemia. The patient failed rapidly and died on July 13, 1931. The outstanding observations post mortem were: marked enlargement of all the lymph nodes, of the liver and of the spleen. The bone marrow was red. The spleen and liver exhibited whitish nodules ranging from 3 mm. to 1 cm. in diameter. On cross-section, some of the lymph nodes were reddish and some whitish. Histologic examination showed that two lesions were present. First, chronic lymphatic leukemia, and second, marked proliferation of the reticulo-endothelial cells, forming intercommunicating strands in the spleen, liver and bone marrow and large nodules in the first two organs. The lymph nodes exhibited lymphatic leukemic lesions and, between the latter, large cell proliferations, bringing about nearly complete compression of the lymphatic tissue. At various points in the aforementioned cell proliferations phagocytosis of granular débris was exhibited, also red cells with pigment formation. In none of the situations were transitions from the lymphatic leukemic cells to the described proliferating cells noted. The lesions were explained as having developed independently along with the chronic lymphatic leukemia.

THE CEREBRAL RESPONSE TO OIL INJECTED INTO THE BRAIN SUBSTANCE IN RABBITS. C. R. TUTHILL and G. M. BECK.

Mineral oil, olive oil and rabbit fat were injected into the brain substance of seventeen rabbits. The animals were put to death from twenty-four hours to fifty-two days after the operations. The earliest reaction appeared to be a retrogressive change in the oligodendroglia bordering the wounds, causing their nuclei to assume the form seen in polymorphonuclear leukocytes. The astrocytes grew

rapidly during the first three days and completed the walling off of the wounds in seventeen days, with but few glia in both radiating and parallel formation. The wounds tended to close with connective tissue and capillary reaction. The microglia produced the same rapid proliferation of fat granule cells as in stab wounds. The transformation of adventitial wall cells to microglia could be traced by the proliferation of adventitial wall cells in the perivascular spaces around twenty-four hour wounds and by the migration of these long, slender cells to the edge of the perivascular nervous tissue. The early migrated adventitial wall cell was characterized by the same morphology as it showed when present in the perivascular space. In wounds from two to five days old, the cells at the edge of the perivascular nervous tissue had increased in size and showed fine, barely perceptible filaments at the poles and from the cytoplasm about the nucleus. Immature bipolar forms with fine processes were also found in the nervous tissue at the edge of the wounds after four days, but elongated cells without processes were seen only at the edge of the perivascular nervous tissue. In older wounds and in uninjured parts of the brain, fully mature tripolar and multipolar cells were found at the edge of the perivascular nervous tissue. Division of fully grown microglia was never seen nor were there found round cells coming from the walls of blood vessels and migrating into the nervous tissue.

A complete report will appear in the *Archives of Neurology and Psychiatry.*

MESENTERIC LYMPHADENECTASIS. JOSEPH M. HILL.

A case of mesenteric lymphadenectasis in a white man, aged 60 years, was reported.

Clinically, the patient exhibited the picture of cachexia with nausea, pain in the epigastrium and frequent bowel movements, but an excellent appetite; this condition had developed over a period of about four months. No diagnosis was made. The patient gradually grew weaker and finally became comatose and died.

Post mortem, all the mesenteric lymph nodes as well as the retroperitoneal lymph nodes were found involved. They exhibited, grossly, a spongy, finely cystic appearance and ranged in size up to 2 cm. in diameter. Microscopically, the cystic appearance differentiated itself into distended, tortuous, communicating lymph node sinuses. The contents consisted of a homogeneous, thick, oily material, which stained red with scharlach R stain, but which was not doubly refractive. Not only were the lymph node sinuses entirely filled and distended by this lipoid substance, but also the lymphatic capillaries and lacteals in the intestinal mucosa.

The cellular elements of these lymph nodes suggested generally a marked response of the reticulum in a proliferation of the reticulum cells with the frequent formation of giant cells. Plasma and mast cells were numerous. The architecture of the lymph nodule was entirely obliterated, leaving only lymphocytic cell collections mingled with the cells described. Most of the nodes showed some few polymorphonuclear leukocytes, but in a number of the particularly smaller ones near the pancreas, the polymorphonuclears were the dominant type of cell; adjacent lymph vessels were found plugged with leukocytes, and a bacterial stain of this tissue showed numerous gram-positive streptococci.

The lymphadenectasis was interpreted as the result of obstruction in the lymphatic system proximal to the lymph nodes, the exact location of which could not be determined.

The cachexia might be accounted for by this obstruction.

Death resulted from the terminal type of hypostatic pneumonia.

A CASE OF GENERALIZED FIBROSIS CYSTICA OF BONE ASSOCIATED WITH TUMOR OF A PARATHYROID GLAND. RAYMOND S. ROSEDALE.

A case of generalized fibrosis cystica of the bone associated with tumor of a parathyroid gland in a white woman, aged 50 years, was presented. The clinical symptoms were marked loss of weight, polyuria, constipation, weakness, fatiga-

bility, and pain over the knees and right tibia. Physical examination revealed a firm nodule in the posterior aspect of the right lower thyroid lobe, emaciation, and tenderness over the calcanea and the right tibia. X-ray pictures revealed cystic areas in the ribs, clavicle, scapulae, tibiae and mandible, vacuolization of the skull, and generalized loss of density of the bones. The blood calcium was 16.5 mg., and the phosphorus 2 mg. per hundred cubic centimeters of blood.

The bone lesion on biopsy showed only osteoid tissue with some vacuolization, many osteoclasts, and active osteoblasts around the margin of the osteoid tissue. There was considerable fibrous tissue interspersed throughout.

The parathyroid tumor on removal was found to measure 2 by 1 by 1 cm. It was yellow in color and firm in consistency, with some cystic areas. The histologic diagnosis was: adenomatous hypertrophy with cystic degeneration of a parathyroid gland.

Acute urinary suppression developed, and the patient died four days after operation. Autopsy was refused.

MASSIVE ATELECTASIS OF THE LUNG FOLLOWING BRONCHIAL OBSTRUCTION BY CALCIFIED TUBERCULOUS TRACHEOBRONCHIAL LYMPH NODES. S. SANES and WARREN S. SMITH.

An unusual case of massive atelectasis with induration of the entire right lung following complete obstruction of the right main bronchus by tuberculous calcified lymph nodes was presented. A white woman, 37 years of age, became ill when she was 22 years old with an acute condition of the right side of the chest. Examination at that time showed dulness and displacement of the heart to the right side. No fluid was obtained on aspiration. In the next fifteen years, the findings in the chest remained unaltered, and provoked the diagnosis of pulmonary tuberculosis with fibrous changes and adhesions, and pleurisy with effusion. On no occasion were tubercle bacilli found in the sputum. Except for a mild dyspnea, the patient suffered little change in her general health. Death was finally due to lobar pneumonia (pneumococcal) of the left lung.

Autopsy revealed complete obstruction of the right main bronchus throughout its whole course, due to complete calcification of the right lower and upper tracheobronchial lymph nodes following tuberculosis, marked collapse-induration of the whole right lung, with total adhesive pleuritis; dextroposition of the heart, compensatory hypertrophy and emphysema of the left upper lobe, an old tuberculous focus in the apex of the left upper lobe, a few tuberculous nodules in the left bronchopulmonary and tracheobronchial lymph nodes, lobar pneumonia with fibrinous pleuritis of the left lower lobe, a few gray tubercles in the liver and left kidney, a slight, firm splenic tumor and bilateral serous cystomas of the ovary.

It is intended to publish a complete report in the *American Review of Tuberculosis*.

PREGNANCY FOLLOWING PROLONGED USE OF RADIUM. LOUIS A. SIEGEL.

The case that I am presenting is of interest from the physiologic, pathologic and clinical aspects. The patient, aged 37, a gravida for the fourth time, gave birth to her last previous child in 1922. For the next five months following her delivery, she had profuse flowing spells, for which she was curetted with the insertion of radium sufficient to produce an amenorrhea for two years. The histologic diagnosis of the scrapings was simple glandular hyperplasia. From 1924 to the time of writing the patient menstruated irregularly, missing from one to two months.

In 1930, she became pregnant. The expected time of delivery was very uncertain, and on Jan. 22, 1931, it was decided, following an examination, to perform a cesarean section. The indication for this procedure was the condition of the cervix, which was found to be markedly contracted and hard. It was believed that the cervix was fibrosed to a point that would not permit sufficient dilatation to allow delivery through the birth canal. At the operation, when the

uterus was cut into, the muscle wall showed evidence of a marked increase of fibrous tissue. A supravaginal hysterectomy was performed and when the cervix was cut across, the fibrosis was very marked, which corroborated the preoperative clinical impression. Both ovaries were markedly shrunken and elongated. A normal, healthy baby, weighing 8 pounds and 8 ounces (3,856 Gm.), was delivered. The postoperative convalescence was uneventful, and at the time of writing the patient is perfectly well.

This case illustrates, first, the injudicious and incorrect use of radium. Secondly, it demonstrates the possibility of the development of normal ova after prolonged interference with this function. This is in accord with the work of Dr. Douglas P. Murphy of Philadelphia, who has shown the effects of the x-rays and radium on animals before, during and after conception. Thirdly, the specimen is of interest as the lower segment and upper part of the cervix show a marked increase in fibrous tissue distributed around each muscle bundle and between the fibers. With a control specimen which had not been subjected to radium, van Gieson sections show a marked increase in the fibrous tissue in the case reported. Fourthly, cesarean section, in all cases presenting similar clinical findings, is the procedure of choice, as shown by histologic examination of the specimen.

This case is being reported by courtesy of Dr. Francis C. Goldsborough.

AN UNUSUAL CASE OF SEVERE PYEMIC EMBOLIC CHOLECYSTITIS WITH MULTIPLE LESIONS IN THE GALLBLADDER LEADING TO PERFORATION AND LOCALIZED PERITONITIS. K. TERPLAN and S. SANES.

The gross specimen and microscopic slides were presented. A complete report will be published in this journal.

Book Reviews

Cytology and Cellular Pathology of the Nervous System. Edited by Wilder Penfield, Professor of Neurology and Neurosurgery, McGill University, Montreal, Canada. Volumes 1, 2 and 3. Cloth. Price, $30 net. Pp. 1,280, with 886 illustrations, 15 in colors. New York: Paul B. Hoeber, Inc., 1932.

This is the third in a series of works on cytology issued by the same publisher, the earlier being the "Handbook on Microscopic Technique," edited by C. E. McClung, and "Special Cytology," edited by E. V. Cowdry, now in its second edition. The present work is dedicated to Ramón y Cajal, the great leader in neurocytology.

The volumes before us are the products of internationally cooperative authorship by twenty-six neurocytologists in Canada, France, Germany, Holland, Spain, Sweden and the United States. The result is a comprehensive exposition in about thirty sections or chapters of the results of modern methods of studying the minute structure of the nervous system, including blood vessels, membranes, nerve sheaths and other structures not necessarily derived from neuro-epithelium. Each of the authors has handled his subject or subjects as seemed best to him. Each section or chapter has its own analytic table of contents, independently numbered illustrations and bibliography. To review each section separately is not feasible, and the most that may be done is to indicate briefly the scope and nature of the contents.

The first two volumes deal with the normal cytology and the general pathologic cytology of the nervous system and related structures, but the complete microscopic anatomy peculiar to any definite disease is not described. The sections come in this order: the general character of the neuron (Cowdry); the principles of the development of the nervous system (Kappers, Amsterdam); sensory ganglions and cranial and spinal nerves, normal and pathologic (de Castro, Madrid); the histopathology of nerve cells (Bielschowsky, Berlin); sheaths of the peripheral nerves, nerve degeneration and regeneration (Nageotte, Paris); nerve endings (de Castro, Madrid); nerves of blood vessels, heart, meninges, digestive tract and urinary bladder (Stöhr, Jr., Bonn); neuroglia, normal and pathologic (Penfield); microglia (del Rio Hortega, Madrid); choroid plexus and ependyma (Agduhr, Uppsala); cerebrospinal blood vessels (Cobb); the meninges, with special reference to the cell covering of the leptomeninges (Weed); pineal gland (del Rio Hortega); the hypophysis (Bucy); retina, choroid and sclera (Arey); the optic nerve and papilla (Cone and MacMillan).

The third volume is devoted to neoplasms, malformation and hematogenous reactions. The sections are as follows: cellular types in primary tumors of the brain (Bailey); tumors of the sheaths of the nervous system (Penfield); primary tumors of the spinal cord and intradural filum terminale (Kernohan); tumors of the optic nerve (Verhoeff); tumors of the retina (Grinker); tumors of the choroid and allied tumors (Friedenwald); neuroblastic tumors of the sympathetic nervous system (Bielschowsky, Berlin); neural proliferations in the vermiform appendix (Masson); tumors of the hypophysis (Bailey); malformation in the central nervous system — tuberous sclerosis, amaurotic family idiocy, aplasia axialis extracorticalis congenita, encephalitis periaxialis diffusa (Globus); hydrocephalus and the atrophy of cerebral compression (Penfield and Elvidge); inflammatory cells in the central nervous system (Greenfield, London); the cells in the cerebrospinal fluid (Boyd).

As pointed out by the editor in his preface, multiple sclerosis, muscular atrophy and other diseases are not considered. In a future edition it may be possible, perhaps, to make the presentation more complete on the pathologic side.

The illustrations merit commendation. They are placed in the text except in the case of the section on the retina, choroid and sclera, which is provided with eighty-three figures on six plates.

New or at least unfamiliar words are not infrequent. As examples that should receive the attention of the medical lexicographer may be mentioned: allocortex, archicortex, clasmatodendrosis, hygrophora, hyperepiphysia, hypo-epiphysia, isocortex, lemnoblasts, neurocrinia, neocortex, oligoglia, pachygyria, paraphysis, pathoclisis, pituicyte, pyronephore, sterocilia, sympathoblastoma, sympathogonia, sympathogonioma.

The pages are numbered consecutively through the three volumes, and there is a general index at the end of the third volume. It would have been advantageous to have indicated on the back of each volume the pages it contains. Of course, this defect may be remedied easily by pasting on the back of volume 2 a slip of paper giving the pages within its covers.

The book will be an invaluable source of information and guidance to the student and to the investigator of normal and pathologic neurocytology. The pathologist will welcome especially the sections on tumors and the illuminating discussions of the new classifications. To quote the editor: "It [the book] presents such insight into the field of future advance as may be granted to those who are contributing seriously to contemporary study of the normal structure and pathological variations of the nervous system."

Microscopic Slide Precipitation Tests for the Diagnosis and Exclusion of Syphilis. By B. S. Kline. Price, $2.50. Pp. 124. Baltimore: Williams & Wilkins Company, 1931.

This book is an illustration of how not to write a laboratory guide dealing with the procedure of only one of numerous tests for the laboratory diagnosis of syphilis and how not to publish a book intended for workers trained in the technological field of one of the most responsible branches of medical laboratory technology. Many controversial issues of importance are dealt with in positive, almost final terms, all favorable to the test of the author. Certain important theoretical phases of the work are dealt with in chapters of 1 or 1½ pages, hardly deserving the dignified name of a chapter. The volume is disproportionately illustrated, and the illustrations are wastefully large. The illustrations on pages 2, 36, 45, 48, 54, 60 and 63 may serve their purposes at an exhibition, but detract from the dignity of the book and reflect on the adequacy of the training of "serologists interested in practical" laboratory work, for whom, according to the author's preface, the volume was ostensibly written. Of the 124 pages (from cover to cover) constituting the volume, 40 are either blank or given to pictures; 12 are given to the preface, table of contents, list of illustrations, references and index, and about 10 are given to table compilations. Less than half of the book is given to solid print. The book, in short, is a hybrid between a grade school self-instructor in manual training and an attempt to give a scientific foundation to a mere modification or improvement of a preexisting serologic technical procedure.

Books Received

THE AETIOLOGY OF TUBERCULOSIS. By Dr. Robert Koch. A translation from the German of the original paper announcing the discovery of the tubercle bacillus, read before the Physiological Society in Berlin, March 24, 1882, and published in the *Berliner klinische Wochenschrift*, 1882, XIX, 221, specially prepared for *The American Review of Tuberculosis*, March, 1932, by Dr. and Mrs. Max Pinner. With an introduction by Dr. Allen K. Krause. Price, cloth, 50 cents. Pp. 48, with 8 illustrations. New York: National Tuberculosis Association, 1932.

NEOPLASMS OF DOMESTICATED ANIMALS. By William H. Feldman, D.V.M., M.D., Division of Experimental Surgery and Pathology, the Mayo Foundation, Rochester, Minn. With a foreword by Charles H. Mayo, M.D. Cloth. Price, $6, net. Pp. 410, with 193 illustrations. Philadelphia, W. B. Saunders Company, 1932.

TECHNIQUES DE LABORATOIRE APPLIQUÉES AUX MALADIES DE LA DIGESTION ET DE LA NUTRITION. Par Labbe, Labbe et Nepveux. Price, 140 francs. Pp. 886. Paris: Masson & Cie, 1932.

A TEXTBOOK OF GENERAL BACTERIOLOGY. By Edwin O. Jordan, Ph.D., Professor of Bacteriology in the University of Chicago and in Rush Medical College. Price, $10. Pp. 819, with illustrations. Edition 10, entirely reset. Philadelphia: W. B. Saunders Company, 1931.

METHODS AND PROBLEMS OF MEDICAL EDUCATION. Series 20, The Rockefeller Foundation, 61 Broadway, New York, 1932.

MASS UND ZAHL IN DER PATHOLOGIE. Von Professor Dr. Robert Roessle, Direktor des Pathologischen Instituts der Universität Berlin und Dr. Frédéric Roulet, Oberarzt am Pathologischen Institut der Universität Berlin. Price, paper covers, 16 marks; bound, 20 marks. Pp. 144. Berlin: Julius Springer, 1932.

THE LIFE OF EDWARD JENNER, M.D., F.R.S., NATURALIST AND DISCOVERER OF VACCINATION. By F. Dawtrey Drewitt. Price, $2. Pp. 127, with portrait. New York: Longmans, Green & Co., 1931.

PRIMARY CARCINOMA OF THE LUNG: BRONCHIOGENIC CANCER: A CLINICAL AND PATHOLOGICAL STUDY. In two parts. By B. M. Fried, M.D., Peter Bent Brigham Hospital, Boston. Price, cloth, $5. Pp. 247, with 95 illustrations. Baltimore: Williams & Wilkins Company, 1932.

MICROSCOPIC SLIDE PRECIPITATION TESTS FOR THE DIAGNOSIS AND EXCLUSION OF SYPHILIS. By B. S. Kline, M.D., Chief of Laboratories, Mount Sinai Hospital of Cleveland, Assistant Professor of Pathology, Western Reserve University. Price, $2.50. Pp. 99. Baltimore: Williams & Wilkins Company, 1932.

HISTOPATHOLOGY OF THE CENTRAL NERVOUS SYSTEM. An Introduction by Means of Typical Microphotographs and a Short Text by Prof. Dr. L. Bouman (Utrecht) and Prof. Dr. S. T. Bok (Leiden). Price, 25 florins. Pp. 37, with 212 illustrations. Utrecht: A. Oosthoek's Publishing Co., 1932.

PHYSIOLOGY OF BACTERIA. By Otto Rahn, Professor of Bacteriology, Cornell University, Ithaca, N. Y. Price, cloth, $6. Pp. 438, with 42 illustrations. Philadelphia: P. Blakiston's Son & Company, Inc., 1932.

TUBERKULOSE ALS SCHICKSAL: EINE SAMMLUNGPATHOGRAPHISCHER SKIZZEN VON CALVIN BIS KLABUND, 1509-1928. Von Dr. Erich Ebstein. Mit einer Einführung von Georg B. Gruber. Price, 6.50 marks; bound, 8 marks. Pp. 184, with 8 tables. Stuttgart: Ferdinand Enke, 1932.

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